Non-small cell lung cancer in the elderly

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Treatment and outcomes in daily clinical practice

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Chapter I

Introduction and outline

Introduction and outline

In the Netherlands, the number of newly diagnosed patients with lung cancer has increased from 8,625 in 1990 to 12,764 in 2015,[1] and almost half is aged 70 years or older.[2] Ageing of the population is expected to further contribute to increasing numbers of older patients with lung cancer.[3]

Etiology and risk factors

The predominant cause of lung cancer is smoking, which has a direct dose-response relationship between the number of cigarettes smoked and the risk of lung cancer.[4] Other behaviour or lifestyle risk factors for lung cancer are low socioeconomic status[5] and preexisting lung disease such as emphysema and chronic obstructive pulmonary disease (COPD).[6] However, smoking is a confounder as it causes lung and cardiovascular diseases as well.[7] Environmental risk factors are second-hand tobacco smoke,[8] fine-particulate air pollution,[9] Radon exposure,[10] and asbestos exposure.[6] In recent years, more insights were gained regarding genetic risk factors. These include inherited genetic polymorphisms (single-nucleotide polymorphisms, SNPs) which can be reflected in the family history[11] and several somatic mutations which are acquired during life.[12] Research mainly focused on mutations present in the EGFR pathway and aberrations in oncogenes ALK, KRAS, HER-2, and ROS1 which affect tumour growth, invasion, and metastasis in lung cells.[12, 13] Also, long-term exposure to exogenous factors and decline of DNA repair mechanisms contribute to the emergence of (lung) cancer among the older population specifically.

Histology and stage of disease

Lung cancer can be divided into two main histology types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The focus of this PhD thesis will be on patients with NSCLC, who comprise 85% of the lung cancer population.[14] NSCLC can be further divided into squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and not otherwise specified (NOS). Squamous cell carcinoma is mainly located in the central airways and used to be the largest proportion of the population,[15] but has decreased from 52% in 1989-1993 to 29% in 2004-2009.[16] Adenocarcinoma, which in general is more peripherally located, has increased from a proportion of 25% in 1989-1993 to 36% in 2004-2009. This could be due to the increasing use of light and filter cigarettes. Also, adenocarcinoma is more frequently present among never smokers and is associated with several oncogenic driver mutations in i.e. the EGFR pathway.[17] Large cell carcinoma is more peripherally located, and this proportion has increased from 21% in 1989-1993 to 34% in 2004-2009. Lung tumours which are poorly differentiated or lack distinctive features are categorized as NOS,[18] and occurred in 2% of patients in 1989-1993 and 1% in 2004-2009.[16]

In literature, patients with NSCLC are mainly described according to stage of disease. These stages are defined according to the anatomic extent of disease in the Tumour Node and Metastasis (TNM) guidelines and determined by location, size (T1-4), and spread to nearby (regional) lymph nodes (N0-3)) or other organs (M0-1)) of the tumour.[19] Perspectives in terms of prognosis are incorporated as well, which can aid treatment planning and assist in the evaluation of treatment results.[20] Trends in the Netherlands indicate that the proportion of patients with stage I NSCLC decreased from 28% in 1989-1993 to 20% in 2004-2009, and slightly increased from 3% to 4 % (respectively) for patients with stage II. Stage I and II together are also called early stage NSCLC. The proportion of patients with locally advanced (stage III) NSCLC decreased from 35% to 30% in respective time periods, whereas the proportion with advanced (stage IV) disease increased from 24% to 44%.[16]

Over time, new insights in prognosis and treatment impacted the TNM classification and renewed editions led to upstaging and downstaging. Upstaging means reclassification to a stage with poorer prognosis (i.e. from stage I in the previous edition to stage II in the new edition), whereas downstaging means reclassification to a stage with better prognosis (i.e. from stage II in the previous edition to stage I in the new edition). This stage migration, also called the Will Rogers Phenomenon, is of key importance to interpret changes in treatment options and survival rates between time periods. Differences could be interpreted as a result of advances in treatment options, distribution of patient characteristics, and diagnostic techniques,[21, 22] whereas it (partially) could be explained by changes in the TNM classification. The first TNM edition was published in 1966. Major revisions were implemented in 1974, in which lung cancer was included as a separate entity for the first time and was based on surgical data of 2,155 lung cancer patients. The third edition was published in 1978, where stage I was divided into Ia (T1-2N0M0) and Ib (T1N1M0), and stage IV was added (TanyNanyM1). In the fourth edition, published in 1987, T1N1M0 was reclassified from stage IB into II and TanyN3M0 and T4NanyMo from stage IV into IIIB. In 1997, the fifth edition was introduced, where patients with T1N0M0 were categorized from stage I to stage Ia, T2N0M0 from stage I to Ib, T1N1M0 from stage II to IIa, and T2N1Mo and T3N0M0 from stage II to IIb.[23] The 6th TNM edition was published in 2002, without changes in staging for lung cancer.[19] However, the 7th edition, published in 2010, was majorly revised and based on a retrospective database of over 100,000 cases of lung cancer with mature outcome. Upstaging was implemented for patients with T2 (>5 but ≤7 cm) NoMo from stage Ib to IIa, T2 (>7cm) N0M0 from stage Ib to IIb, T2 (>7cm) N1M0 from stage IIb to IIIa, and malignant pleural involvement from stage IIIb to IV. Furthermore, downstaging occurred for patients with T2 (≤5cm) N2 from stage IIb to IIa, separate tumour nodes in the same lobe (N0) from stage IIIb to IIb, N1-2 from stage IIIb to IIIa, separate tumour nodes in different ipsilateral lobes (N0-1) from stage IV to IIIa, N2-3 from stage IV to IIIb, and for T4 (extension) N0-1Mo from stage IIIb to IIIa.[24]

Treatment options and outcomes in patients with NSCLC

Treatment guidelines for patients with NSCLC are based on evidence from literature and discussion by national and international collaborating experts in the field. Since 2004, the Dutch national guideline for patients with NSCLC was implemented and initiated by the Dutch Lung Cancer Study Group.[25] Throughout the years, results of clinical trials provided new insights and after reaching consensus with experts in the field, standard and alternative treatment options in the Netherlands were adapted in 2011,[26] and in 2015 (table 1).[27] Before treatment decision-making is performed, detailed staging of the tumour according to the TNM guidelines is necessary (see *Histology and stage of disease*), as well as pretreatment risk assessment together with prediction of post-treatment status.[28] As therapeutic interventions negatively affect pulmonary and vascular reserve capacity, the predicted tolerance of treatment can be estimated on forehand by examination of these capacities, performance status, comorbid conditions, relative risk of morbidity and mortality after treatment, ability to cope with potential negative side effects, and the preservation of quality of life.[28] Standard treatment options are mainly based on the treatment resulting in the best survival and local control rates per disease stage, which are based on evidence from patients participating in clinical trials. However, outcomes of individual patients in clinical practice may differ because standard treatment is regularly paired with severe adverse events in more than half of patients,[29] unplanned hospitalizations,[30] dose reduction, functional decline,[31] and premature discontinuation of treatment.[32] As a result, the full curative potential of complete treatment regimens cannot always be achieved, leading to poorer survival rates.

Patients with stage I and II NSCLC show the best survival rates, with 5-year survival rates of 63% for stage I and 44% for stage II disease.[33] Standard radical treatment is surgical resection for stage I, with the addition of postoperative radiotherapy in case of unforeseen N2 disease for both stage I and II. Fit patients (Performance Status (PS) o-1) with stage II NSCLC are advised to undergo surgery with adjuvant chemotherapy for tumours >4cm or N1 disease.[27, 34] An alternative treatment option for inoperable patients or those not accepting surgery-related risks is stereotactic body radiotherapy (SBRT) for stage I and II NSCLC. While hypofractionated high-dose radiotherapy is not specifically stated in guidelines, it can be offered.[28] Moreover, recent randomized controlled trials (RCTs) show that outcomes between SBRT and surgery for operable patients with stage I NSCLC are comparable.[35]

Table 1 Overview of standard and alternative treatment options according to Dutch treatment guidelines for patients with stage I-IV non-small cell lung cancer

	Stage I	Stage II	Stage III	Stage IV
Since 2004 (1) **Standard**	*Surgery* - PORT *	*Surgery* - PORT *	*Sequential CHRT*	*BSC* and *CT* †
Alternative	*Conventional RT*	*Conventional RT*	*Concurrent CHRT* † ‡ *Radical RT* *BSC* and *CT* † §	
Since 2011 (2) **Standard**	*Surgery* - PORT *	*Surgery* - PORT * - adjuvant CT †	*Concurrent CHRT* † ‡ *Surgery* - adjuvant CT †	*CT* †† *EGFR-TKI* **
Alternative	*SBRT* ¶	*SBRT* ¶	*Sequential CHRT* *EGFR-TKI* § ** - adjuvant CT	
Since 2015 (3) **Standard**	*Surgery* - PORT *	*Surgery* - PORT * - adjuvant CT †	*Concurrent CHRT* † ‡*Surgery* - adjuvant CT †	*CT* †† - immunotherapy *EGFR-TKI* ** - adjuvant CT *ALK-TKI* ** - immunotherapy
Alternative	*SBRT* ‡‡	*SBRT* ‡‡	*Sequential CHRT* *EGFR-TKI* § ** - adjuvant CT *ALK-TKI* §**	

(1) Dutch Lung Cancer Study Group. Guidelines Non-small cell lung cancer. Oncoline. Version 1.0; 2004
(2) National Collaboration for Lung Tumours. Guidelines Non-small cell lung cancer. Oncoline Version 2.0; 2011
(3) National Collaboration for Lung Tumours. Guidelines Non-small cell lung cancer. Oncoline. Version 2.3; 2015

Symbols: * when unforeseen N2, † PS 0-1, ‡ unresectable disease, § stage IIIB NSCLC, ¶ inoperable patients with peripheral tumour ≤5cm without lymph node metastases , ** first-line treatment if aberration present, †† PS 0-2, ‡‡ inoperable patients with peripheral or central tumours

Abbreviations: Oncoline (Oncology Online (Dutch)), ESMO (European society for medical oncology), VATS (video-assisted thoracic surgery), CT (chemotherapy), PORT (postoperative radiotherapy), CHRT (chemoradiotherapy), PS (performance status), SBRT (stereotactic body radiotherapy), RT (radiotherapy), BSC (Best Supportive Care)

Stage III NSCLC is the most heterogeneous patient group, ranging from T4N0M0 to TanyN3Mo with a 5-year survival rate of 19%.[33] Treatment choice depends on resectability of the tumour and operability of the patient, and most patients are inoperable or have unresectable disease. Standard treatment for this group is chemoradiotherapy, which preferably is concurrently administered.[28, 36, 37] Although 5-year survival rates up to 35% are seen among patients receiving concurrent chemoradiotherapy, this treatment is also associated with high risk of complications compared to alternative treatment options. Standard treatment for resectable disease among operable patients is surgery with neo- or adjuvant CT, depending on resectability or completeness of resection, involvement of nodes, and size of the tumour. For patients who are not deemed fit enough for these standard treatment options or who decline combination treatments, alternative treatment options with curative intent are sequential chemoradiotherapy[27, 38] and radical radiotherapy, although the latter is not explicitly stated in guidelines.[39] For patients with stage III disease, adjuvant immunotherapy agents provide promising perspectives: The 'Pacific trial' indicated that patients receiving immunotherapy adjuvant to concurrent chemoradiotherapy had significantly higher progression-free survival compared to those

receiving chemoradiotherapy with a placebo. Secondary outpoints favored immunotherapy as well, and data on survival are pending.[40] The 3-year survival rate of patients with stage IV NSCLC is only 5%.[33] As the intent of treatment is to palliate and focus on quality of life, pretreatment risk assessment includes complete medical history, smoking history, comorbid conditions, weight loss, performance status, and physical examination. All patients with PS 0-2 should be offered chemotherapy.[41] Marked advances have been achieved in recent years due to the application of TKIs among patients with driver mutations. Recent studies including patients with EGFR aberrations receiving EGFR-TKI's showed 2-year survival rates of 66% and 5-year survival rates of 15%.[42] Since 2011, first-line treatment with EGFR-TKI's followed by chemotherapy is considered standard treatment for eligible patients.41 Patients with ALK aberrations benefit most from ALK-TKI's and 2-year survival rates of 66% have been seen.[43] Therefore, ALK-TKI's are considered standard treatment for patients with ALK aberrations since 2015.[27] Second line treatment with immunotherapy has become standard care since 2016 as overall survival, response rate, and progression-free survival were significantly better compared to chemotherapy alone.[44] Improvements in patient selection indicated significantly better outcomes in first-line treatment with immunotherapy among those with PDL1 expression in >50% of tumour cells as compared to chemotherapy alone.[45] Furthermore, a combination of chemotherapy and immunotherapy showed significantly higher survival among those without specific oncogenes compared to chemotherapy alone.[46] These treatment strategies are not yet implemented in (inter)national treatment guidelines, but stated as standard of care by the Dutch association of pulmonologists.

Older patients with lung cancer: a unique population

There is no universal definition for 'older' patients in the medical field. The European Society for Medical Oncology (ESMO) and the International Society of Geriatric Oncology (SIOG) state that chronological age should be seen in the context of each individual's biological age, as there is marked variability within and between older patients with (lung) cancer. Biological age is an indicator or reflection of the remaining life expectancy and functional reserves, and includes age-related changes leading to reduced organ and cognitive function. Nevertheless, the age cut-off point of 70 years is practical and the most commonly used within the field of geriatric oncology.[47]

A significant proportion of newly diagnosed patients with NSCLC are of older age. In the Netherlands, the median age of patients with NSCLC is 70 years.[48] Moreover, trends in time indicate that the proportion of patients aged 75 years and older increased slightly from 24% in 1989-2003 to 26% in 2004-2009.[16] Studies indicate that a large proportion of patients with NSCLC aged 70 years or older do not receive (curative-intent) treatment with complex reasons.[49, 50] Consequences of smoking go beyond the initiation of lung cancer alone, and can affect biological age tremendously. Comorbid conditions, such as COPD and cardiovascular disease,[51] occur frequently and indirectly lead to polypharmacy.[52] Furthermore, poor performance status, malnutrition, and an inactive lifestyle are common as well. [29, 53-55] Additionally, geriatric issues such as mobility, independence, vulnerability, patients living alone, and functional disability could affect treatment outcomes.[51, 53, 54, 56, 57] However, these cognitive and age-related organ deteriorations are often undiagnosed, and can be more complex than estimated at first.[58, 59]

As a result, these important factors could influence treatment outcomes and can weigh in treatment decisions.[2, 38, 57, 60-63] Overtreatment could result into adverse events, unplanned hospitalizations, early termination of treatment, and decreased quality of life,[38, 63-66] whereas undertreatment can lead to shorter survival in relatively fit patients. Also, preferences and wishes of both patients and caregivers regarding treatment options, effects, and quality of life, are important for treatment decision-making.[38, 67] Therefore, decision-making based on chronological age alone is insufficient for this heterogeneous group of elderly.

Evidence for treatment decision-making among older patients with lung cancer is scarce. A review of 419 clinical trials including patients with lung cancer showed that strict inclusion and exclusion criteria are handled regarding organ function (76%), PS (57%), and age (13%), leading to explicit and implicit exclusion of older patients with lung cancer. Only nine trials (2%) were specifically designed for those aged 70 years or older, where eight stated organ function restrictions and nine explicitly excluded patients with PS 3 or 4. Ultimately, relatively young and fit patients with no or mild comorbid conditions were included in these elderly-specific trials.[68] This group does not represent the average older patient in daily clinical practice.[16, 37, 68] Also, elderly-specific studies often close early due to slow accrual.[35] On the other hand, trials that include both older and younger patients often do not perform analyses for elderly specifically. Also, the resulting subgroups are too small to draw conclusions, which probably leads to overestimation of treatment effects among elderly. This strengthens the importance of observational studies as insights can be gained into patterns of treatment and survival among older and frail patients as well.

The European Organization for Research and Treatment of Cancer (EORTC) Elderly Task Force and Lung Cancer Group collaborated with SIOG in order to provide an experts' opinion consensus regarding the treatment of elderly with lung cancer.[51] Although data are limited regarding patients aged ≥80 years, those with stage I-II NSCLC should not be denied surgical treatment based on chronological age alone. Also, adjuvant chemotherapy is associated with survival benefits. SBRT could represent an alternative treatment in case of inoperability. For elderly with stage III NSCLC, concurrent or sequential chemoradiotherapy can be considered in selected, fit patients only. The use of carboplatin-based doublets in fit elderly with stage IV NSCLC is supported, while less fit patients should be offered single-agent treatment. The effects of bevacizumab in combination with chemotherapy were unclear up until the paper in 2014, although toxicity is expected to be higher among elderly compared to younger patients. However, older patients with EGFR mutations are strongly recommended to receive EGFR-TKI's as first line treatment, although chemotherapy is preferred as first-line treatment for those with wild-type EGFR. Overall, second-line treatment should not be denied based on age alone. Furthermore, a comprehensive geriatric assessment (CGA) is strongly recommended for treatment decision-making,[51] which is also recommended by SIOG since 2005.[69, 70]

The CGA, also called geriatric assessment when referring to the diagnostic process only, is an important tool for investigating biological age and patient's preferences extensively. The aim of the CGA is to determine the medical, psychosocial, and functional capabilities of older patients in a multidimensional and interdisciplinary diagnostic process to distinguish fit and frail patients and to develop a coordinated and integrated treatment plan for long-

term follow up.[70] The CGA investigates possible deficiencies regarding cognitive status, anxiety and depression, social support, dependency, mobility, physical capacity, activities of daily living (ADL), Instrumental ADL (IADL), nutritional status, comorbidity, and polypharmacy. Improvements in outcomes were previously demonstrated when CGA is incorporated in the treatment decision-making process among other geriatric patients with cancer.[71, 72] For patients with lung cancer specifically, a single center study in the Netherlands indicated that 78% of patients undergoing CGA suffered from geriatric impairments, where nutritional impairments occurred most often (52%). In 58% of these patients, the impairments that came to light by CGA were previously undiagnosed, and 43% suffered from ≥3 geriatric impairments.[59] Furthermore, systematic evidence indicated that 75% of patients received non-oncologic interventions after CGA, and treatment plans were altered in 45% of patients after CGA.[73] Nevertheless, CGA is also thought of as time-consuming as it brings about both extra time and costs during diagnostic work-up.[74] Therefore, several shorter tools or screening instruments have been developed and might be more practical to use in clinical practice. Examples are the World Health Organization (WHO) PS, Short Physical Performance Battery (SPPB), Timed-Up and Go Test (TUG), International Classification of Functioning (ICF), Groningen Frailty Indicator (GFI), and Geriatric8 (G8). However, the discriminative power between frail and fit patients by screening instruments as compared to CGA is generally lower. Also, several important impairments can be missed. It is challenging to select the optimal treatment strategy, [70, 71] and as a result, treatment decisions can differ widely within the heterogeneous population of older patients with NSCLC.

Lifestyle programs for patients with NSCLC

As mentioned previously, many patients with NSCLC suffer from a poor general condition before treatment, and often experience adverse events and further functional decline during treatment.[29, 30] This is partly due to the intensity of treatment options and aggressiveness of disease, but also due to an inactive lifestyle.[55] Physical training additional to medical treatment could optimize physical parameters, leading to better tolerance of intensive treatment.[75, 76] This can be achieved by prehabilitation (therapeutic training before undergoing treatment)[77] and rehabilitation (therapeutic training during and after treatment).[78] The physiological reserve can be expanded by a combination of resistance and endurance training. Even better outcomes could be achieved when the diet is adapted to the needs of training as well, including healthy and high protein food.[79] This leads to increased resilience and a safety margin to meet potential enlarged demands of cardiac output at the time of surgery or chemotherapeutic agents.[62, 77] Nevertheless, patients with NSCLC are often vulnerable and both intramural training (within the hospital) and extramural training (centers outside the hospital and home) could arise additional barriers to adhere to medical treatment or lifestyle programs due to i.e. commuting constrains.[76, 80] Therefore, personal training sessions at home or adjacent to hospital appointments could enhance patient motivation and exercise adherence as several barriers are taken away. As a result, patients can profit more from the curative potential of medical treatment and quality of life.[76] However, feasibility and effects of prehabilitation and rehabilitation for patients with NSCLC are still unclear.

Promising directions: aims and outline of this thesis

Despite major advances in the last decades regarding knowledge of treatment options and survival for patients with NSCLC, evidence for treatment and outcomes among older patients in daily clinical practice remains highly needed. As older patients are frequently excluded from clinical trials, observational studies can provide valuable insights in this expanding and heterogeneous population. The aims of this thesis are to investigate patterns of treatment and survival in older patients compared to younger patients, and within elderly with NSCLC. Also, reasons for omitting standard treatment and detailed patient characteristics predictive for treatment tolerance and survival are explored. Furthermore, current practice of geriatric assessment and treatment selection in daily clinical practice is investigated. Effects of prehabilitation and rehabilitation among patients receiving curative-intent treatment are included as well, and focus on physical performance, treatment tolerance, adherence, and quality of life.

More specifically, **part 1** addresses population-based data concerning patterns of treatment and survival in the Netherlands, with a focus in **chapter 2** on the comparison of trends in treatment and relative survival between patients <70 years and those aged ≥70 years with NSCLC in 25 years. In **chapter 3**, treatment and overall survival of patients aged ≥65 years with stage I NSCLC are compared between two time periods. In **chapter 4**, patients with stage I and II NSCLC aged 65-74 years are compared to those aged ≥75 years regarding treatment and overall survival. **Chapter 5** addresses patients with stage III NSCLC regarding treatment and overall survival, where patients aged 65-74 years are compared to those aged ≥75 years. In **chapter 6**, patients with lung cancer aged ≥85 years are compared to those aged 71-84 years and those aged ≤70 years, regarding diagnostic work-up, treatment, and overall survival. **Part 2** (**chapter 7**) focuses on treatment options, treatment tolerance, and survival among patients with stage III NSCLC aged ≥70 years, including motives for omitting standard treatment and patient factors related to treatment tolerance and overall survival. In **part 3**, additional interventions that could improve treatment selection and outcomes for patients with NSCLC in daily clinical practice are addressed. In **chapter 8**, the integration of geriatric assessment for older patients with NSCLC is investigated in hospitals in the Netherlands. Systematic evidence for prehabilitation and rehabilitation among patients with NSCLC is reviewed, focusing on a home-based component and physical activity in **chapter 9**, and aiming on quality of life and fatigue after prehabilitation among patients undergoing surgery in **chapter 10**. The innovativity, challenges, and future perspectives of these findings are discussed in **Part 4**.

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Part I

Population-based data regarding treatment and survival

Chapter 2

Trends in treatment and relative survival among Non-Small Cell Lung Cancer patients in the Netherlands (1990–2014): Disparities between younger and older patients

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Abstract

Background: This study aimed to describe trends over time regarding disparities in treatment and relative survival (RS) between younger and older patients with non-small cell lung cancer (NSCLC).

Methods: All patients diagnosed with pathologically verified NSCLC in 1990-2014 were included from the Netherlands Cancer Registry (n=187,315). Treatment and RS (adjusted for sex, histology, treatment) were analyzed according to age group (<70 years versus ≥70 years), stage, and 5-year period of diagnosis.

Results: Between 1990 and 2014, 5-year RS increased from 17% to 22% among younger patients and from 12% to 16% among elderly. The application of surgery increased over time for elderly with stage I NSCLC, decreased for elderly with stage II, and was stable but higher for younger patients. Disparities in RS between age groups with stage I became smaller since 2000-2004, but did not change over time for stage II. For stage III and IV, both age groups showed strong increases over time in chemoradiotherapy and chemotherapy from 2000 onwards, although considerably less among elderly. One-, 3- and 5-year RS increased more strongly over time for the younger group leading to larger disparities between age groups with stage III or IV NSCLC.

Conclusion: More curative-intent treatment and improved RS for NSCLC were seen over time, but were less profound among elderly. Disparities herein between age groups seemed to become smaller over time for stage I NSCLC, did not change for stage II, and were widening for stage III and IV at the expense of elderly. Future prospective studies should focus on optimizing treatment selection and outcomes for elderly.

Introduction

Survival of non-small cell lung cancer (NSCLC) has improved significantly between 1989 and 2009.[1] A Dutch population-based study found that more than 60% of patients with NSCLC younger than 75 years received standard treatment, whereas this was only 20% for those aged 75 years and older.[1]Elderly with NSCLC suffer particularly from smoking-related comorbidities, poor performance status, and inactivity.[2-4] As these factors can affect patient mobility, treatment tolerance, and survival,[5-8] older and high-risk patients are often excluded from standard therapy and clinical trials.[9] Therefore, evidence is scarce for curative-intent treatment options in elderly.[10-12] It is unclear whether older patients with NSCLC have taken advantage of new detection and treatment options over time in the same way as younger patients.

This study focuses on describing trends and disparities over time in treatment, relative survival (RS), and the contribution of treatment towards changes in relative excess risk of mortality (RER) between younger and older patients with NSCLC over the last 25 years in the Netherlands, according to patient and tumour characteristics.

Methods

Population-based data from the nationwide Netherlands Cancer Registry were used. Since 1989, almost all newly diagnosed cancer patients were included, with a completeness rate of >95% and complete national coverage. Trained registrars routinely collect data from medical records such as patient and tumour characteristics and primary treatment. According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry.

Information on all patients with primary invasive lung cancer between 1990 and 2014 was retrieved. Patients with small cell lung cancer, carcinoid tumours, absence of pathological verification, or incidental diagnosis at autopsy were excluded (supplemental figure 1). The International Classification of Disease for Oncology (ICD-O) was used to code topography (C34) and morphology (invasive 8010-8020, 8022-8035, 8046-8230, 8243-8246, 8250-8576, 8972, 8980-8982, and 9110). Between 1986 and 1992, the first edition was used,[13] and between 1993 and 1994 an adapted version for the Netherlands became available (ICD-O "N").[14] The second edition was also adapted for the Netherlands and handled between 1995 and 2000 (ICD-O2).[15] Since 2001, the third edition adapted for the Netherlands was handled, including the updates to the International Classification of Diseases for Oncology since 2012 (ICD-O3).[16, 17] TNM (Tumour Node Metastases) guidelines[18] were used for tumour staging and derived from the postsurgical TNM and supplemented with the clinical TNM. At the Netherlands Cancer Registry, edition 4 of the TNM guidelines was applied up to 1992, edition 4 (2nd edition) from 1993 to 1998, edition 5 from 1999 to 2002, edition 6 from 2003 to 2009, and edition 7 from 2010 onwards. Stage of disease was classified as I, II, III, IV or unknown. Unknown stage of disease was not further issued

for analyses. Histology was sub-classified as adenocarcinoma, squamous cell carcinoma, large cell carcinoma and other NSCLC (including not otherwise specified NSCLC).[19] Age was categorized as younger patients (<70 years), and older patients or elderly (≥70 years). This demarcation point was chosen since the incidence of age-related changes sharply increases in those aged 70 years and older.[20] Years of diagnosis were divided into 5-year periods from 1990 to 2014. Primary treatment was categorized as surgery with or without (neo)adjuvant therapy, radiotherapy (RT), chemotherapy (CT), chemoradiotherapy (CHRT, including radiotherapy with sensitizer, CT prior to RT, or RT prior to CT), Best Supportive Care (BSC), other (including targeted therapy) and unknown. Concurrent and sequential CHRT could not be distinguished for analyses, as time between treatments was often unavailable, especially in earlier years. Curative-intent treatment included surgery (with or without (neo)adjuvant therapy) and CHRT. RT has not been included as curative-intent treatment as radical and palliative RT could not be distinguished for all patients. Information on vital status was initially obtained from municipal registries and hospitals and since 1995 from the nationwide population registries network. Follow-up was completed and calculated from the time of diagnosis until death or until February 1st 2016. RS was displayed as median, 1-year, and 5-year RS rate. For stage IV NSCLC, 3-year instead of 5-year RS rate was displayed. RS was considered a proxy for lung cancer-specific survival, as it is divided by age and sex-specific overall survival of the general Dutch population, thereby eliminating the effect of other causes of death.

Multivariable RS analyses, using Poisson regression modeling,[21]were performed to calculate the specific Relative Excess Risk (RER) of death estimates with corresponding 95% Confidence Intervals (95%CI).The RER displays trends of the risk of mortality for the given period compared to the reference period 1990-1994. These trends are compared between younger and older patients and stratified by stage. Adjustments for the influence of sex and histology were performed in model 1. Additional adjustment for treatment was performed in model 2 in order to investigate the effect of treatment on the RER of mortality over time. When model 1 and 2 are compared, and the RER moves more towards 1.0 by ≥ 0.10 after additional adjustment for treatment, differences in RER became smaller compared to the reference group and might be explained by treatment. This means that treatment might have contributed to decreased excess risk in the given time period. Whether disparities between age groups are widening or narrowing over time was determined by comparing age groups with respect to trends in proportions of curative-intent treatment, improvements in RS, changes in RER (model 1), and the contribution of treatment on these changes (model 2). All analyses were performed using SAS 9.4.

Results

In the Netherlands, 187,315 patients were diagnosed with NSCLC between 1990 and 2014 of whom 44% was aged ≥70 years. Over time, the proportion of males was highest and decreased less in older compared to younger patients (Table 1). Squamous cell carcinoma occurred more frequently among elderly and decreased in both age groups over time, whereas adenocarcinoma increased over time.

The proportion of stage IV NSCLC increased strongly since 2000-2004, while stage I and III decreased slightly in both age groups. Over time, curative-intent treatment was more often administered in all patients, although this remained clearly lower among elderly (Table 2). Between 1990 and 2014, 5-year RS increased from 17% to 22% among younger patients, and from 12% to 16% among elderly (Figure 1, median RS displayed in Supplementary table 1). Also, the RER in both age groups was significantly lower in 2010-2014 as compared to 1990-1994, even after adjustment for sex, histology, and treatment. These decreases in RER over time were slightly stronger for younger patients compared to elderly (Table 3). Detailed results of all stages of NSCLC are described below.

For stage I, both the application of surgery and RT increased slightly over time, whereas BSC decreased noticeably. Despite strong increases over 25 years, elderly received remarkably less surgery compared to the younger group. One-year RS increased relatively more over time among elderly, even as for 5-year RS. Since 2000-2004, the RER decreased significantly compared to 1990-1994 in both age groups. In 2010-2014, the RER was significantly lower among older (RER 0.49) compared to younger patients (RER 0.62). After additional adjustment for treatment, differences in RER between younger and older patients disappeared (Table 3, model 2).

Table 1. Characteristics of all patients diagnosed with non-small cell lung cancer between 1990 and 2014 in the Netherlands according to 5-year period of diagnosis and stratified for younger (<70 years) and older patients (≥70 years)

	Younger patients (n=105,417)					Older patients (n=81,898)				
Period of diagnosis	**1990-**	**1995-**	**2000-**	**2005-**	**2010-**	**1990-**	**1995-**	**2000-**	**2005-**	**2010-**
Demographics	**1994**	**1999**	**2004**	**2009**	**2014**	**1994**	**1999**	**2004**	**2009**	**2014**
Total n	18,484	19,219	19,723	22,703	25,288	14,255	14,667	15,178	17,911	19,887
Sex n (%)										
Male	14793	14147	12959	13339	14793	12652	12423	11928	13109	13655(69)
Female	(80)	(74)	(66)	(59)	(80)	(89)	(85)	(79)	(73)	6232(31)
	3691 (20)	5072 (26)	6764 (34)	9364 (41)	3691 (20)	1603 (11)	2244 (15)	3250 (21)	4802 (27)	
Median age yrs	62	62	60	61	62	75	75	75	75	76
Histology n(%)										
Squamous CC	8709 (47)	7575 (39)	6270 (32)	5699 (25)	6153 (24)	8179 (57)	7156 (49)	6066 (40)	6113 (34)	7152 (36)
Adenocarcinoma	5540 (30)	6567 (34)	7162 (36)	9553 (42)	14399	2886 (20)	3632 (25)	4179 (28)	5866 (33)	8877 (45)
Large CC	2608 (14)	3782 (20)	4410 (22)	4392 (19)	(57)	1866 (13)	2775 (19)	3377 (22)	3477 (19)	1559 (8)
Other NSCLC	1627 (9)	1295 (7)	1881 (10)	3059 (13)	2064 (8)	1324 (9)	1104 (8)	1556 (10)	2455 (14)	2299 (12)
					2672 (11)					
Stage n (%)										
I	4219 (23)	4079 (21)	3426 (17)	3940 (17)	3881 (15)	4077 (29)	3998 (27)	3181 (21)	3621 (20)	3355 (17)
II	1298 (7)	1325 (7)	1471 (7)	1379 (6)	2099 (8)	781 (5)	770 (5)	1020 (7)	1074 (6)	1934 (10)
III	7043 (38)	7252 (38)	6522 (33)	6540 (29)	6354 (25)	5053 (35)	5330 (36)	5261 (35)	5574 (31)	4942 (25)
IV	5199 (28)	5968 (31)	7970 (40)	10621	12843	2935 (21)	3455 (24)	5138 (34)	7354 (41)	9481 (48)
Unknown	725 (4)	595 (3)	334 (2)	(47)	(51)	1409 (10)	1114 (8)	578 (4)	288 (2)	175 (1)
				223 (1)	111 (0.5)					

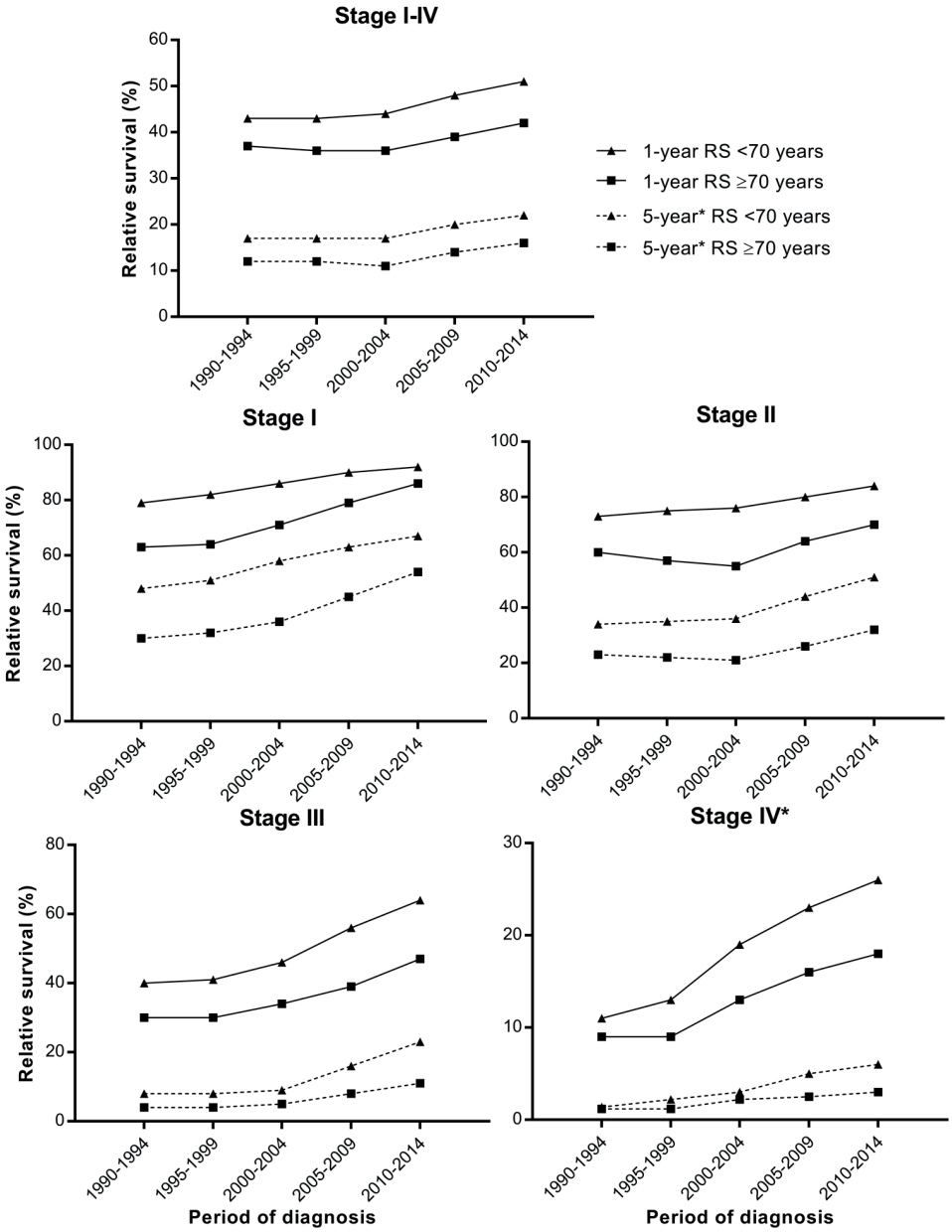
Abbreviations % 'Percentage', CC 'Cell Carcinoma', n 'number', NSCLC 'Non-Small Cell Lung Cancer', yrs 'years'; All demographics differed significantly between periods of diagnosis within age groups (P<0.0001)

Table 2. Administered treatment options of all patients diagnosed with non-small cell lung cancer between 1990 and 2014 in the Netherlands according to 5-year period of diagnosis, stage of disease and stratified for younger (<70 years) and older patients (≥70 years)

		Younger patients (n=105,417)					Older patients (n=81,898)				
Stage	**Period of diagnosis** **Treatment*****	**1990-1994**	**1995-1999**	**2000-2004**	**2005-2009**	**2010-2014**	**1990-1994**	**1995-1999**	**2000-2004**	**2005-2009**	**2010-2014**
I	Surgery*	3237 (77)	3243 (80)	2758 (81)	3159 (80)	3088 (80)	1842 (45)	1918 (48)	1688 (53)	2051 (57)	1849 (55)
	RT	495 (12)	405 (10)	238 (12)	325 (16)	582 (15)	1204 (30)	1116 (28)	771 (24)	904 (25)	1164 (35)
	BSC	291 (7)	321 (8)	183 (5)	152 (4)	101 (3)	905 (22)	901 (23)	599 (19)	485 (13)	259 (8)
II	Surgery*	1064 (82)	1109 (84)	1066 (72)	989 (72)	1568 (75)	482 (62)	500 (65)	529 (52)	539 (50)	960 (50)
	RT	78 (6)	78 (6)	102 (7)	82 (6)	121 (6)	151 (19)	139 (18)	250 (25)	227 (21)	467 (24)
	BSC	47 (4)	86 (6)	64 (4)	55 (4)	87 (4)	105 (13)	111 (14)	171 (17)	167 (16)	275 (14)
III	CHRT	102 (1)	541 (7)	1674 (26)	2421 (37)	3068 (48)	14 (0)	102 (2)	520 (10)	1044 (19)	1336 (27)
	Surgery*	1181 (17)	1120 (15)	795 (12)	763 (12)	879 (14)	484 (10)	504 (9)	404 (8)	434 (8)	448 (9)
	RT	3821 (54)	3047 (42)	1199 (18)	540 (18)	389 (6)	2680 (53)	2456 (46)	1701 (32)	1017 (18)	929 (19)
	CT	322 (5)	1027 (14)	1664 (25)	1764 (27)	1164 (18)	55 (1)	172 (3)	553 (11)	905 (16)	666 (13)
	BSC	1272 (18)	1311 (18)	1041 (16)	866 (13)	647 (10)	1627 (32)	1893 (36)	1905 (36)	1927 (35)	1436 (29)
IV	CT	426 (8)	1057 (18)	2534 (32)	3924 (37)	4543 (35)	53 (2)	179 (5)	798 (16)	1499 (20)	1979 (21)
	RT**	1405 (27)	1068 (18)	776 (10)	615 (6)	551 (4)	722 (25)	663 (19)	655 (13)	552 (8)	642 (7)
	Other	275 (5)	120 (2)	128 (2)	318 (3)	519 (4)	135 (5)	73 (2)	108 (2)	288 (4)	424 (5)
	BSC	2842 (55)	3463 (58)	4044 (51)	5226 (49)	6664 (52)	1949 (66)	2448 (71)	3402 (66)	4843 (66)	6239 (66)

Numbers are displayed as number with percentages (%); Abbreviations BSC 'Best Supportive Care', CHRT 'Chemo-radiotherapy', CT 'Chemotherapy', n 'Number', RT 'Radiotherapy', yrs 'years'; * with or without (neo)adjuvant therapy; **RT on primary tumor; ***Patients can receive combinations of treatments; Cumulated percentages could be lower than 100% as treatment options with low proportions were not included in this table

Figure1. Relative survival rates of all patients diagnosed with non-small cell lung cancer between 1990 and 2014 in the Netherlands according to 5-year period of diagnosis, stage of disease, and stratified for younger (<70 years) and older patients (≥70 years) *3-year relative survival for stage IV



For stage II, the proportion of patients undergoing surgery decreased from 2000-2004 onwards. Elderly underwent considerably less surgery, more RT, and more BSC compared to younger patients. Initially, RS increased relatively more over time among younger patients, but elderly seemed to catch up since 2005-2009. The RER decreased significantly since 2005-2009 and this decrease was more pronounced in younger compared to older patients, even after adjustment for treatment (RER 0.58 for <70 and RER 0.73 for ≥70 (Table 3, model 2)).

For stage III, the application of CHRT increased strongly since 2000-2004 but remained considerably lower among elderly. The proportion of patients in both age groups undergoing surgery remained stable over time, CT increased, and RT decreased, whereas BSC decreased in younger patients only. The improvement in RS over time was more pronounced in younger compared to older patients. Although the RER decreased over time in both age groups, this was stronger among younger (RER 0.54) compared to older patients (RER 0.61 (Table 3, model 1)). This difference disappeared after adjustment for changes in treatment over time (2010-2014: RER 0.78 for <70 and 0.81 for ≥70 (Table3, model 2)).

For stage IV, both age groups received CT considerably more since 2000-2004. However, elderly received BSC more often than younger patients. Median, 1-year and 3-year RS increased since 2000-2004 in both age groups, although this increase was stronger among younger patients. Decreases in the RER over time were seen in both age groups, but were stronger among younger patients (RER 0.65 for <70 and 0.70 for ≥70 (Table 3, model 1)). After adjustment for changes in treatment over time, the decrease in RER over time remained stronger for younger patients (RER 0.72 for <70 and 0.82 for ≥70 (Table 3, model 2)).

Discussion

The aim of this study was to describe trends and disparities in treatment patterns, RS, and the contribution of treatment towards changes in RER over time between younger and older patients with NSCLC according to patient and tumour characteristics. In stage I-III, curative-intent treatment was administered more often over time, even as CT for stage IV NSCLC. Also, RS improved considerably over time, both in the total group as in all separate stages. Overall, these trends were less pronounced among elderly,[22, 23] which might be explained by high-risk characteristics,[6, 8] therapeutic nihilism by high age,[24] lack of evidence for treatment options due to exclusion of elderly in trials, and slow accrual in studies specifically aimed at elderly.[5, 9, 25] Patients could also prefer less intensive treatment, as good quality of life is cherished instead of longer survival time.[5, 26] A previous population-based study found promising trends in progress for patients with NSCLC over time up to 2009.[1] Our study indicated continued progress in curative-intent treatment, RS, and RER adjusted for treatment in 2010-2014, although less profound among elderly.

The increasing incidence of NSCLC diagnoses since 2000-2004 could be explained by the rise in popularity of smoking 30 to 40 years prior.[27] However, cancer is a disease

of the elderly and the expanding population as well as ageing will have contributed to higher cancer incidence over time.[28] Increases in curative-intent treatment and RS could be explained by improvements in detection and treatment options over time. Furthermore, increased awareness of worthwhile treatment options and the availability of treatment guidelines in the Netherlands since 2000-2004, could partly explain these increases as well. Nevertheless, stage migration (the so-called Will Rogers phenomenon) might also play a role,[29, 30] and could lead to selection of good prognosis patients and upstaging of those with worse prognosis. This could result in seemingly more curative-intent treatment and improved survival for separate stages. However, RS in the current study increased for all patients independent of stage. This was somewhat more pronounced for younger patients (5% increase in 5-year RS over time) as compared to elderly (4% increase in 5-year RS over time). Furthermore, changes in the classification of stage of NSCLC by TNM guidelines over 25 years may also have impacted available treatment options and prognosis for each stage and both age groups.[31]

Table 3. Multivariate relative survival with Relative Excess Risk of all patients diagnosed with non-small cell lung cancer between 1990 and 2014 in the Netherlands according to 5-year period of diagnosis and stage of disease, and stratified for younger (<70 years) and older patients (≥70 years)

		Younger patients (n=105,417)				Older patients (n=81,898)			
Stage	**Period of**	**Model 1**		**Model 2**		**Model 1**		**Model 2**	
	diagnosis	**RER**	**95%CI**	**RER**	**95%CI**	**RER**	**95%CI**	**RER**	**95%CI**
All	1990-1994	*Ref*		*Ref*		*Ref*		*Ref*	
	1995-1999	0.98	0.96-1.00	0.95	0.93-0.98	0.98	0.95-1.01	1.02	0.99-1.04
	2000-2004	0.94	0.92-0.97	0.96	0.94-0.98	0.97	0.95-1.00	1.03	1.01-1.06
	2005-2009	0.82	0.80-0.84	0.81	0.79-0.82	0.82	0.80-0.84	0.91	0.89-0.93
	2010-2014	0.92	0.90-0.94	0.81	0.79-0.83	0.89	0.87-0.92	0.90	0.88-0.93
I	1990-1994	*Ref*		*Ref*		*Ref*		*Ref*	
	1995-1999	0.93	0.87-1.00	0.87	0.82-0.93	0.95	0.89-1.00	0.93	0.87-0.98
	2000-2004	0.76	0.71-0.82	0.78	0.72-0.83	0.81	0.76-0.87	0.85	0.80-0.91
	2005-2009	0.66	0.61-0.71	0.62	0.58-0.83	0.58	0.64-0.62	0.64	0.60-0.68
	2010-2014	0.62	0.57-0.67	0.54	0.50-0.58	0.49	0.45-0.53	0.49	0.45-0.53
II	1990-1994	*Ref*		*Ref*		*Ref*		Ref	
	1995-1999	0.95	0.86-1.05	0.84	0.76-0.93	1.04	0.92-1.19	1.04	0.92-1.19
	2000-2004	0.92	0.84-1.02	0.87	0.79-0.97	1.08	0.95-1.21	1.08	0.96-1.22
	2005-2009	0.72	0.65-0.80	0.66	0.59-0.74	0.85	0.75-0.96	0.82	0.73-0.93
	2010-2014	0.63	0.57-0.70	0.58	0.53-0.65	0.80	0.71-0.90	0.73	0.65-0.82
III	1990-1994	*Ref*		*Ref*		*Ref*		*Ref*	
	1995-1999	0.98	0.95-1.02	1.02	0.99-1.06	0.97	0.93-1.01	0.98	0.94-1.03
	2000-2004	0.86	0.83-0.89	1.07	1.03-1.12	0.86	0.82-0.90	0.97	0.93-1.01
	2005-2009	0.63	0.61-0.66	0.88	0.85-0.92	0.69	0.66-0.72	0.87	0.83-0.91
	2010-2014	0.54	0.52-0.57	0.78	0.74-0.81	0.61	0.58-0.63	0.81	0.77-0.85
IV	1990-1994	*Ref*		*Ref*		*Ref*		*Ref*	
	1995-1999	0.90	0.86-0.93	0.92	0.89-0.96	0.96	0.91-1.01	0.98	0.93-1.03
	2000-2004	0.73	0.70-0.76	0.84	0.81-0.87	0.78	0.75-0.82	0.91	0.86-0.95
	2005-2009	0.63	0.61-0.65	0.72	0.69-0.74	0.71	0.68-0.74	0.83	0.80-0.87
	2010-2014	0.65	0.63-0.67	0.72	0.70-0.75	0.70	0.67-0.74	0.82	0.78-0.86

Numbers are displayed as N 'number' with 95%CI '95% confidence interval'; Abbreviations Ref 'Reference'; Model 1 adjusted for sex and histology; Model 2 adjusted for sex, histology and treatment

For stage I, the application of surgery and RT among elderly increased over time, even as RS. Extensive collaboration between medical specialties for treatment decision-making and the influence of patient's wishes could have contributed.[32] Also, stage migration and revisions by the 7th edition of TNM guidelines could have resulted into selection of patients with a predominantly good prognosis, as those with stage IB and worse prognosis were upstaged to stage IIA, leading to seemingly more curative-intent treatment and improved RS.[33] Although advances in treatment options like the rising application of Video Assisted Thoracic Surgery and Stereotactic Ablative Radiotherapy[34] could explain improved RS, especially for older patients, this could not be confirmed yet.[35] Together, elderly seem to be catching up on younger patients and disparities became smaller over time for patients with stage I NSCLC.

For stage II, surgery decreased but remained the most often administered treatment option for both age groups. The application of RT and BSC were higher among elderly as compared to the younger group. Patients migrated up to stage II from stage IB since 1999[36], and down from stage IIIA since 2010[33], leading to a heterogeneous patient group . This could explain lower resection rates,[1] and increased application of CHRT up to 9% and 7% among younger and older patients in recent years, respectively. Although younger patients showed earlier improvements in one-year RS, elderly seem to catch up modestly, whereas the contribution of treatment for changes in RS remains uncertain in both age groups. Nevertheless, disparities did not change over time for stage II NSCLC.

For stage III, the introduction and increasing application of CHRT could have led to improved RS and decreased RER in younger patients, as implementation increased sharply from 2000-2004 onwards. Although the application of CHRT also increased among elderly, this remained considerably lower compared to younger patients. Awareness of treating older patients is rising in recent years, whereas treatment options remain limited in vulnerable patients.[11, 37]This might be explained by lack of evidence for treatment options in older and vulnerable patients,[38] patients not being fit enough, fear of adverse events, or patients' refusing therapy.[37] Also, the implementation of the PET/CT-scan and upstaging of stage IIIB could have led to migration of those with worse prognosis to stage IV and thus contributed to improved survival for patients with stage III and IV over time.[30, 33, 39] Together, increased use of curative-intent treatment seemed to contribute to improved RS and RER. However, less improvement was seen for treatment and RS among elderly, leading to widening disparities between age groups for stage III NSCLC.

For stage IV, BSC remained the most common administered treatment for both age groups. The application of CT increased strongly over time, although considerably less among elderly. This could be explained by CT becoming standard treatment for stage IV NSCLC in Dutch guidelines since 2004, with elderly benefiting slightly later.[40] Previous increases in the administration of CT could be assigned to positive results in clinical trials, leading to earlier application in clinical practice. Still, the proportion of CT was expected to be higher in younger patients, as was seen in a previous study of the Netherlands Cancer Registry.[41] Our results affirm that decreased RER over

time seems to be explained partially by increased application of CT. However, it should be considered that diagnosis by PET/CT scan were recommended by Dutch guidelines for the diagnosis and treatment of lung cancer since 2004 in order to identify previously undetected metastases,[42] and together with changing TNM-guidelines[31, 33] considerably more patients with stage IV and a relatively good prognosis were diagnosed.[31]This might partially explain increased 1-year RS among stage IV patients as well.[43] Better survival could also be explained by those with single organ metastases having a favourable prognosis, especially in case of low TN status.[44] Nevertheless, improvements in 3-year RS were scant in both age groups. As poor performance status and comorbidities can contraindicate CT, it was expected that elderly showed less improvements over time.[2] Targeted therapies and other promising treatments are emerging, but concern a small proportion of patients and were not further issued in the current study. Although increases in the administration of CT and improvements in 1-year RS were seen for younger patients, disparities between age groups were widening for treatment, RS, RER, and the RER adjusted for treatment among those with stage IV NSCLC.

Strengths of this study are the nationwide coverage of Dutch patients diagnosed with NSCLC from 1990-2014 and the large number of patients included (n=187,315), without exclusion of specific subgroups. Also, this is the first population-based study describing treatment patterns and RS focusing on disparities between patients aged <70 years and ≥70 years with NSCLC over a period of 25 years. Nevertheless, certain limitations should be mentioned. Some information could not be extracted from the medical records. For instance, smoking habits, and social factors were unknown and comorbid conditions and performance status were unavailable for most patients, which could provoke unknown biases.[2, 37] Treatment details like start and end dates, type of CT, and type of RT were often lacking, especially in earlier years. As a result, concurrent and sequential CHRT as well as conventional RT and stereotactic RT could not always be distinguished. In earlier years, CHRT was coded by CT and RT separately. In more recent years, a distinctive code for CHRT was implemented at the Netherlands Cancer Registry. As acquired treatment was retrieved and toxicity data were not available, it is possible that combined treatments such as CHRT were intended in clinical practice, while toxicities inhibited further treatment, leading to the administration of CT only instead of (intended) CHRT in clinical practice. This could explain the relatively high rate of CT as compared to CHRT for patients with stage III NSCLC, as treating these patients by CT only is uncommon practice and not logical.[37, 45] Also, TNM classification guidelines could have been adopted earlier for treatment decision-making in clinical practice (the 5th and 7th editions became available in 1997 and 2009, respectively), than they were implemented at the Netherlands Cancer Registry (in 1999 and 2010, respectively). Nevertheless, it was assumed that this equally impacted older and younger patients. Follow-up was completed until February 2016, leading to smaller proportions of patients diagnosed in 2012-2014 with complete 5-year follow-up. Also, censoring could occur more among younger patients with stage I and II NSCLC.

In order to maximize treatment effects and continue progress in curative-intent treatment and RS for all patients in the future, vulnerable patients within the older and entire population of NSCLC should be distinguished more carefully. Upcoming prospective studies should include older and vulnerable patients as well, and incorporate predictive patient and tumour factors such as comorbidity and additional geriatric information for older patients. This is essential to optimize treatment selection and survival for all patients with NSCLC.

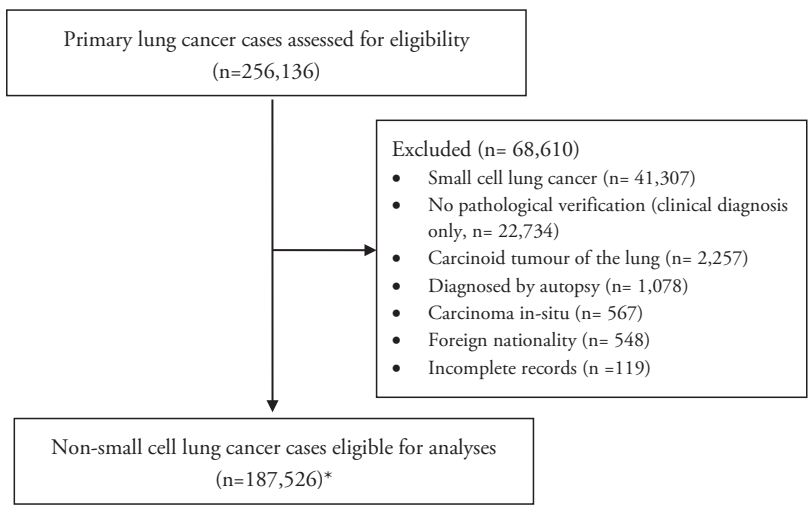
In conclusion, this population-based study gained insights into age-specific trends in clinical practice and subsequent disparities between older and younger unselected patients with NSCLC. The application of curative-intent treatment and RS increased over time for all patients, but remained less profound among elderly. Although improvements in RS for specific stages could be explained by alterations in staging procedures and guidelines for treatment over time, significant improvements in both RS and RER were seen for the whole patient group. Disparities between older and younger patients in patterns of treatment and RS over time seemed to narrow for patients with stage I NSCLC, did not change for stage II, and became wider for patients with stage III and IV at the expense of elderly. Future prospective studies should specifically focus on predictive factors to optimize selection of elderly for curative-intent treatment in order to improve survival.

Supplementary table 1. Median relative survival of all patients diagnosed with non-small cell lung cancer between 1990 and 2014 in the Netherlands according to 5-year period of diagnosis, stage of disease and stratified for younger (<70 years) and older patients (≥70 years)

	Younger patients (n=105,417)					Older patients (n=81,898)				
Period of diagnosis Stage	**1990-1994**	**1995-1999**	**2000-2004**	**2005-2009**	**2010-2014**	**1990-1994**	**1995-1999**	**2000-2004**	**2005-2009**	**2010-2014**
All	9.0 (8.8-9.3)	9.1 (8.9-9.3)	9.6 (9.4-9.9)	11 (11-11)	12 (NA)	6.7 (6.5-7.0)	6.3 (6.1-6.5)	6.3 (6.1-6.4)	7.1 (6.9-7.4)	8.0 (7.7-8.2)
I	44 (41-47)	52 (48-56)	70 (66-76)	85 (82-92)	NA	16 (15-17)	17 (16-19)	22 (21-24)	34 (32-37)	47 (44-50)
II	25 (23-28)	27 (24-29)	28 (25-30)	38 (33-43)	58 (52-64)	16 (33-43)	13 (12-15)	13 (12-14)	18 (16-19)	22 (20-23)
III	9.0 (8.7-9.3)	9.3 (9.0-9.6)	11 (10-11)	14 (13-14)	18 (17-18)	6.4 (6.2-6.7)	6.4 (6.2-6.6)	6.9 (6.6-7.2)	8.1 (7.7-8.4)	10 (9.8-11)
IV	3.5 (3.3-3.6)	3.6 (3.5-3.8)	4.5 (4.4-4.7)	5.3 (5.2-5.5)	5.7 (5.5-5.8)	2.6 (2.4-2.8)	2.6 (2.5-2.8)	3.0 (2.8-3.1)	3.2 (3.1-3.4)	3.4 (3.3-3.5)

Median relative survival is displayed in months with corresponding 95% Confidence Interval; Abbreviations NA 'Not Applicable'

Supplementary figure 1 Flow chart of eligible patients with non-small cell lung cancer.



* This number can slightly deviate from the finally included number of cases as some cases could be added to the database after initial data retrieval for this study

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Chapter 3

Changes in treatment patterns and survival among elderly with stage I non-small cell lung cancer: the introduction of stereotactic body radiotherapy and thoracoscopic surgery

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Abstract

Background: The optimal treatment of elderly patients with early stage non-small cell lung cancer (NSCLC) remains elusive. Still, the introduction of video-assisted thoracic surgery (VATS) and stereotactic body radiotherapy (SBRT) may have led to more elderly receiving treatment and improved median overall survival (OS).

Materials and Methods: We analyzed data from the Netherlands Cancer Registry of 2168 patients ≥65 years with clinical stage I NSCLC and distinguished two periods: 2004-2008 (A) and 2009-2013 (B). The analyses focused on treatment patterns and median OS for patients receiving surgery, radiotherapy, or neither surgery nor radiotherapy. Furthermore, we explored the influence of the application of VATS and SBRT.

Results: The resection rate did not differ between periods A and B (51% vs 53%; p=0.37), despite significantly more VATS procedures in the latter period (0% vs 32%; p<0.001). Application of radiotherapy increased (26% vs 33%; p=0.001), especially SBRT (3% vs 63%; p<0.001). The proportion of patients receiving neither therapy decreased (23% vs 14%; p<0.001). Median OS for all patients significantly improved (31 vs 42 months; p=0.001), and also for those receiving radiotherapy (23 vs 33 months; p=0.02), but not significantly for surgical patients (65 vs 74 months; p=0.16). Still, in multivariable analysis surgical patients had an increased risk of death in period A compared to period B (HR 1.20; 95% CI, 1.01-1.43), this was not the case for patients receiving radiotherapy (HR 1.19; 95% CI, 0.99-1.43). Five-year OS was 57% for surgical patients, and 23% for those receiving radiotherapy.

Conclusion: In elderly patients with stage I NSCLC, the use of surgery remained constant, that of radiotherapy increased, and fewer patients received neither treatment over the years. Median OS improved for all patients; surgery was associated with the highest long-term OS.

Introduction

Lung cancer is the leading cause of cancer death worldwide[1] and in the Netherlands.[2] The highest incidence rates are found among women aged 65-69 years, and among men aged 70-74 years.[3] On the basis of demographic developments the absolute number of new cases of lung cancer in the Netherlands is expected to increase by 46% for men and 24% for women between 2015-2040.[4] Only small improvements in overall survival (OS) have been reported so far. Driessen et al. found that the 5-year relative survival for patients ≥70 years in the Netherlands had increased from 12% in 1990-1994 to 16% in 2010-2014.[5]

Surgery offers the best potential cure for early stage non-small cell lung cancer (NSCLC). It is not always offered, however, to elderly patients in view of their advanced age and comorbidities.[6] In a study by Palma et al., thirty-eight percent of 875 patients ≥75 years with stage I NSCLC did not receive any form of treatment.[7] The outcome of surgery can potentially be improved by video-assisted thoracic surgery (VATS).[8] In previous studies, VATS was superior to thoracotomy in terms of postoperative morbidity, even in octogenarians.[9-11] For patients who are inoperable due to comorbidities, radiotherapy is an alternative treatment with curative intent.[8] Shirvani et al. reported that stereotactic body radiotherapy (SBRT) offers better long-term OS than does external-beam radiotherapy.[12] SBRT makes use of high doses of radiation in a limited number of fractions, thereby avoiding damage to organs close to the tumour.[13] In a study by Haasbeek et al., the application of SBRT in Dutch patients ≥75 years with stage I NSCLC was associated with a 9-month improvement in OS over the period 2001-2009.[8]

New technologies, such as VATS and SBRT, have gained acceptance by now. The question is, however, whether treatment is offered to more elderly patients now and whether the OS has improved. To answer this question, we performed a study evaluating changes in treatment patterns and OS for patients ≥65 years with clinical stage I NSCLC.

Materials and Methods

Population-based data from the southern region of the Netherlands Cancer Registry (NCR) were used. This region covers 2.4 million inhabitants (15% of the Dutch population). The NCR records data of all patients newly diagnosed with cancer. The NCR automatically receives notifications of all newly diagnosed malignancies from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA). Additional sources are radiotherapy institutes and the Dutch national registry of hospital discharge. These data are supplemented with data from medical records, including patient characteristics (such as age, sex, and comorbidities) and tumour characteristics (such as date of diagnosis, tumour type, histology, stage, and treatment). Type of surgery is recorded in the database, whereas details of radiotherapy such as dose or fraction are missing. We selected data from the southern region because information on comorbidities is routinely collected in this region only. Information on vital status was obtained from the population registries network. Cause of death was not available. Follow-up data were complete until February 2017.

We retrieved data of all patients ≥65 years diagnosed between 2004-2013 with clinical stage I NSCLC, according to the International Union Against Cancer Tumour Node Metastasis (TNM) edition 6 and 7 (from 2010 onwards). Treatment patterns and median OS were assessed for two periods: 2004-2008 (period A), and 2009-2013 (period B). In 2004, fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning has been incorporated in the national guideline for NSCLC in the Netherlands. PET-scans were introduced gradually in the Netherlands and became more common practice between 2005-2008. Endoscopic ultrasound (EUS)/endobronchial ultrasound (EBUS) has become more common in daily clinical practice since 2010 and was incorporated in the national guideline in 2011. In the Netherlands, SBRT became available in 2003 and became widespread after 2007.[8] In 2006, the first VATS lobectomy was performed in the Netherlands.[14] Treatment was classified as surgery, including thoracotomy and VATS; radiotherapy, including conventional radiotherapy and SBRT; or neither of these. Patients in the latter category were offered chemotherapy, targeted therapy or best supportive care. Demographic variables retrieved were age and sex. Age was dichotomized as 65-74 years and ≥75 years. Comorbidities were grouped as cardiac, vascular, pulmonary, diabetes, or previous malignancy. Tumour characteristics included clinical tumour stage, histology (adenocarcinoma, squamous cell carcinoma, and other), and the presence or absence of histopathologic confirmation. Dutch national radiotherapy guidelines indicate that patients without pathologic confirmation receive radiotherapy in case of (a) a new or growing lesion on CT scans with characteristics of malignancy; (b) a high risk for developing lung cancer based on age and smoking history; and (c) a FDG-PET-positive lesion.[15] The probability of benign disease in these patients is only 4.3%.[16] Criteria to perform lung surgery were in accordance with the Dutch practice guidelines for the treatment of NSCLC.[17]

Statistical analysis

Baseline differences between the two treatment periods on the one hand, and the three treatment groups on the other hand, were compared using the $X2$ test. Kaplan-Meier estimates of median OS were calculated and the log-rank test was used to detect significant differences. Specific factors associated with an increased hazard ratio (HR) of death were determined with Cox regression analysis. A number of candidate factors were selected on the basis of a statistically significant association with an increased HR of death in previous studies. These were: age,[12] sex,[12] clinical tumour stage,[7] histopathologic confirmation,[7] and a more recent period in time[7, 8]. In addition, the following factors expected to be associated were included: cardiac, vascular, and pulmonary comorbidities, a history of diabetes, and a previous malignancy. A HR > 1.0 with a 95% confidence interval (CI) completely > 1.0 indicates a significant worse outcome. All statistical tests were two-sided, and $p \leq 0.05$ was considered to indicate statistical significance. Statistical analyses were performed using SPSS statistical software (SPSS version 22; Chicago, IL).

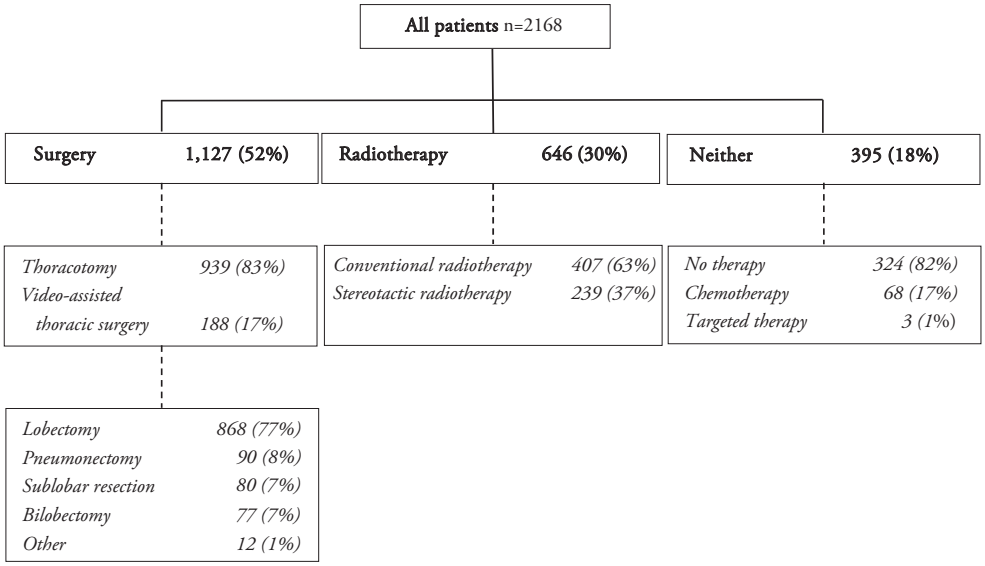

Figure 1. CONSORT diagram of patients ≥65 years diagnosed with clinical stage I NSCLC and primary treatment between 2004 and 2013. Numbers displayed as number (percentage)

Results

Between 2004-2013, a total of 2168 patients ≥65 years (1068 in period A and 1100 in period B) with clinical stage I NSCLC were diagnosed in the southern region of the Netherlands (Figure 1). In period A, no VATS resections were performed and SBRT was offered to nine patients. The mean age was 73.8 (standard deviation 5.7) years, and 30% were female. Median follow-up was 37 months for the entire group, and 52 months, 29 months, and 12 months for patients receiving surgery, radiotherapy, and neither treatment, respectively.

Table 1. Baseline characteristics of patients ≥65 years with clinical stage I NSCLC treated with surgery, radiotherapy, or neither

	Surgery		Radiotherapy		Neither	
Characteristics	**Period A (n=543)**	**Period B (n=584)**	**Period A (n=281)**	**Period B (n=365)**	**Period A (n=244)**	**Period B (n=151)**
Age, n (%)						
65-74 years	**418 (77)**	**412 (71)**	**105 (37)**	**166 (46)**	94 (39)	45 (30)
≥75 years	**125 (23)**	**172 (29)**	**176 (63)**	**199 (54)**	150 (62)	106 (70)
Male sex, n (%)	391 (72)	395 (68)	**209 (74)**	**234 (64)**	173 (71)	108 (72)
Comorbidities, n (%)						
Cardiac	**171 (32)**	**206 (35)**	108 (38)	151 (41)	**88 (36)**	**76 (50)**
Vascular	128 (24)	144 (25)	86 (31)	122 (33)	68 (28)	44 (29)
Pulmonary	**176 (33)**	**210 (36)**	165 (59)	212 (58)	115 (47)	73 (48)
Diabetes	78 (14)	90 (15)	51 (18)	69 (19)	40 (16)	27 (18)

	Surgery		Radiotherapy		Neither	
Previous malignancy	**93 (17)**	**150 (26)**	**58 (21)**	**106 (29)**	56 (23)	37 (25)
Unknown	**13 (2)**	**45 (8)**	7 (3)	19 (5)	6 (3)	8 (3)
cT stage, n (%)						
1	**234 (43)**	**298 (51)**	**53 (19)**	**172 (47)**	**23 (9)**	**28 (19)**
2	245 (45)	235 (40)	**103 (37)**	**98 (27)**	109 (45)	56 (37)
Unknown	64 (12)	51 (9)	**125 (44)**	**95 (26)**	112 (46)	67 (44)
Histology pretreatment						
Adenocarcinoma	**251 (46)**	**228 (39)**	68 (24)	70 (19)	64 (26)	30 (20)
Squamous cell carcinoma	**192 (35)**	**261 (45)**	**29 (10)**	**62 (17)**	**15 (6)**	**18 (12)**
Other	100 (18)	95 (16)	184 (66)	233 (64)	165 (68)	103 (68)
Histopathologic confirmation, n (%)	543 (100)	584 (100)	90 (32)	92 (25)	83 (34)	45 (30)

Statistics in bold indicate a statistical significant difference between period A and B (p≤0.05)

Surgical patients were younger and had statistically significant less often cardiac, vascular, and pulmonary comorbidities than patients in the other groups. Pathological upstaging was documented for 206 patients (18%) after surgery; cT1-2 became pT3-4 in 52 patients, and cN0 became pN1-2 in 171 patients. Seventeen patients were upstaged to pT3-4 and pN1-2. Adjuvant treatment was administered to 92 upstaged patients (45%); 61 patients received chemotherapy, 26 received radiotherapy, four underwent chemoradiation, and one patient was treated with targeted therapy. No histopathologic proof of malignancy was obtained in 72% of patients receiving radiotherapy and 68% of patients receiving neither treatment.

The results are generally consistent with a trend toward greater proportions of patients with comorbidities in period B (Table 1). The proportion of surgical patients with cardiac and pulmonary comorbidities, as well as a previous malignancy had even significantly increased. An aging phenomenon was seen: twenty-three percent of surgical in period A were aged ≥75 years versus 29% in period B (p=0.01). The opposite held for patients receiving radiotherapy: sixty-three percent of patients in period A were aged ≥75 years versus 54% in period B (p=0.04).

The resection rate did not differ between periods A and B (p=0.37, Figure 2), although in period B almost one third of surgical patients had been treated with VATS, versus nil in period A (p<0.001). The application of radiotherapy had increased (p=0.001), especially SBRT (3% vs 63%; p<0.001). In period B, fewer patients than in period A had received neither treatment modality (p<0.001).

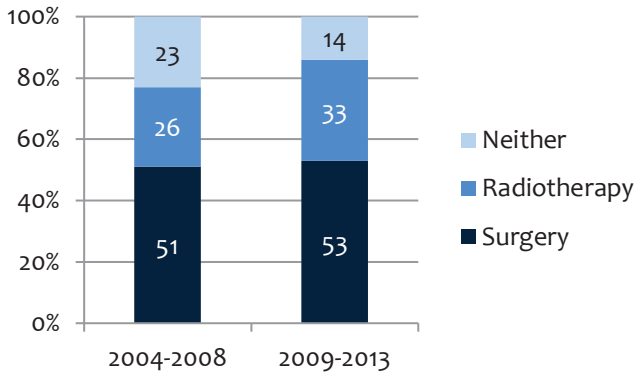

Figure 2. Treatment patterns among patients ≥65 years with clinical stage I NSCLC diagnosed between 2004 and 2013

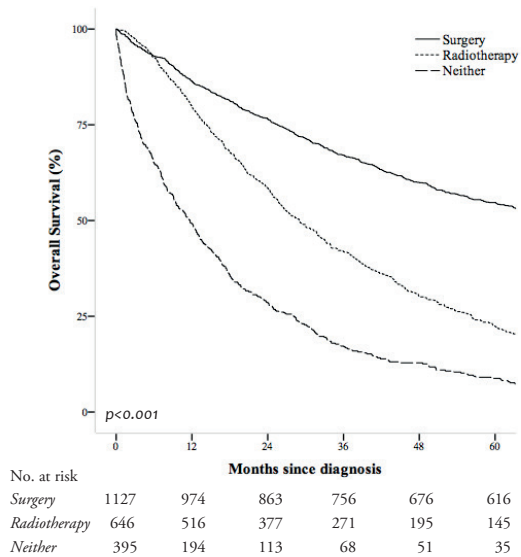

Figure 3. Overall survival for patients ≥65 years with clinical stage I NSCLC by primary treatment (2004-2013)

The estimated median OS time for surgery, radiotherapy, and neither therapy, respectively, was 69 months, 29 months, and 12 months (p<0.001). Long-term OS was better for patients who underwent surgery (p<0.001; Figure 3). Figure 4 shows Kaplan-Meier estimates of the OS in either time period. The median OS for all patients had increased from 31 months to 42 months (p=0.001); that for surgical patients, from 65 months to 74 months (p=0.16). The two-year and five-year OS for surgical patients was 75% and 52%, respectively, in period A, and had for patients receiving radiotherapy, the median OS was 23 months in period A and 33 months in period B (p=0.02). Their two-year and five-year OS had improved statistically significantly from 48% and 21%, respectively, in period A, to 66% and 23% in period B. The median OS for patients receiving neither treatment had declined from 12 months in period A to 11 months in period B (p=0.98).

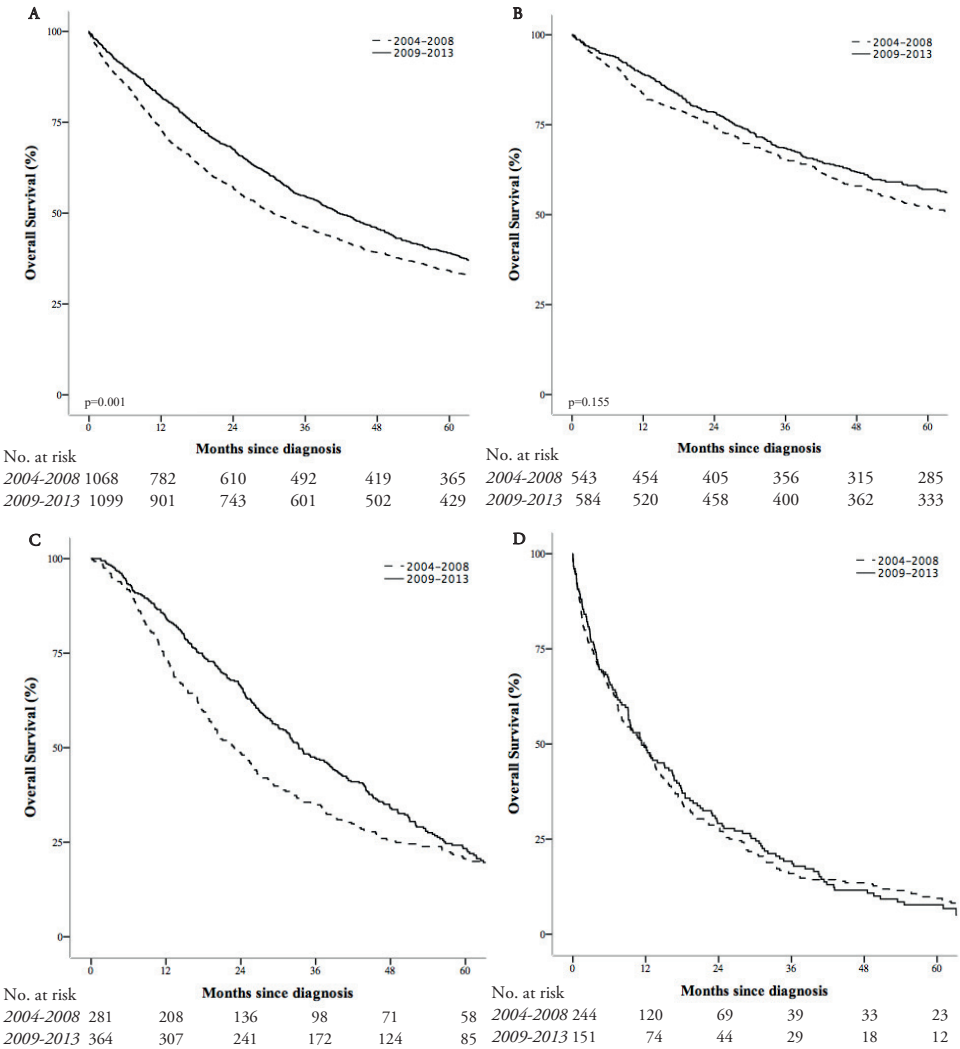

Figure 4. Overall survival for patients ≥65 years with clinical stage I NSCLC by time period. (A) All patients; (B) surgical patients; (C) patients treated with radiotherapy; (D) neither therapy

The adjusted hazard of death had increased over time among all patients ≥75 years (HR 1.49; 95% CI, 1.34-1.66), as well as among all individual subgroups of patients ≥75 years (Table 2). Hazards of death had also increased in all patients with cardiac and pulmonary comorbidities, diabetes, and a previous malignancy, as well as in the subgroup of surgical patients. Among all patients, no histopathologic proof of malignancy was associated with an increased risk of death (HR 1.64; 95% CI, 1.43-1.87). The opposite was true for patients receiving radiotherapy (HR 0.76; 95% CI, 0.61-0.94). For all patients, treatment in period A was associated with a higher hazard of death in comparison with period B. This held for the subgroup of surgical patients as well, but not for patients receiving radiotherapy.

Univariable analysis of clinical T stage demonstrated that T2 disease was associated with an increased risk of death in all patients, as well as the subgroups of patients receiving surgery and radiotherapy.

Table 2. Multivariable analysis of factors associated with an increased hazard of death for elderly patients with clinical stage I NSCLC by primary treatment.

	All patients		Surgery		Radiotherapy		Neither	
Characteristics	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Age								
65-74 years	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
≥75 years	**1.49**	**1.34-1.66**	**1.33**	**1.12-1.58**	**1.25**	**1.04-1.49**	**1.35**	**1.07-1.69**
Gender								
Female	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Male	**1.15**	**1.03-1.29**	**1.27**	**1.06-1.53**	1.00	0.82-1.21	1.11	0.87-1.40
Comorbidities								
Cardiac	**1.22**	**1.10-1.35**	**1.21**	**1.03-1.42**	**1.25**	**1.04-1.49**	1.03	0.83-1.27
Vascular	1.09	0.98-1.22	1.06	0.89 -1.26	1.06	0.89-1.28	1.25	0.99-1.57
Pulmonary	**1.19**	**1.07-1.32**	**1.20**	**1.02 -1.41**	**1.20**	**1.01-1.44**	1.10	0.89-1.36
Diabetes	**1.14**	**1.00-1.30**	**1.29**	**1.05-1.59**	**1.27**	**1.02-1.58**	0.96	0.72-1.26
Previous malignancy	**1.16**	**1.03-1.30**	**1.42**	**1.19-1.71**	0.93	0.76-1.14	1.00	0.78-1.28
Histology pretreatment								
Adenocarcinoma	0.91	0.79-1.05	0.90	0.72-1.12	1.11	0.87-1.42	0.95	0.70-1.28
Squamous cell carcinoma	**0.85**	**0.74-0.99**	1.02	0.81-1.27	0.96	0.74-1.24	0.90	0.59-1.38
Other	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Histopathologic confirmation								
Yes	1 (ref)				1 (ref)		1 (ref)	
No	**1.64**	**1.43-1.87**			**0.76**	**0.61-0.94**	0.98	0.74-1.31
Period								
2004-2008	**1.23**	**1.10-1.37**	**1.20**	**1.01-1.43**	1.19	0.99-1.43	1.03	0.82-1.29
2009-2013	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
cT stage*								
1	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
2	**1.53**	**1.36-1.72**	**1.39**	**1.18-1.63**	**1.50**	**1.22-1.85**	1.14	0.83-1.58

*Due to too many unknown cases (n=514), cT stage is not included in the multivariable analysis. The results shown for cT stage are from a univariable analysis. Statistics in bold indicate a statistical significant difference

Discussion

This study demonstrates a shift in treatment pattern and median OS between 2004-2013 in patients ≥65 years with clinical stage I NSCLC. The resection rate remained constant over time, although the latter period was characterized by a fair number of VATS procedures, versus nil in the former period. The proportion of patients receiving radiotherapy, especially the application of SBRT, had increased significantly in the latter period and therefore the proportion of patients receiving neither therapy decreased. The median OS in the total patient population had significantly increased. In surgical patients the median OS as well as the two-year and five-year OS were higher compared to those receiving radiotherapy.

Although not statistically significant, the median OS of patients who underwent surgery had improved with 9 months in the latter four-year period. Use of surgery remained constant between the time periods while surgical patients were treated at a higher age and the comorbidity burden had increased in the latter period. Pulmonary and cardiac comorbidities, as well as higher age are associated with higher mortality rates and lower OS rates in NSCLC patients.[9, 18] The risk of death had increased in surgical patients with pulmonary and cardiac comorbidities, which might explain why the OS had not statistically significantly improved. Still, after adjustment for the factors in the multivariable model, statistical significance of OS improvement was shown, as surgical treatment in period A was associated with an increased risk of death. The increased adjusted risk of death in period A is likely due to the fact that no VATS procedures were performed during this period. Indeed, Zhang et al. showed significant better long-term OS rates following VATS in a meta-analysis on studies comparing open with VATS lobectomy for early stage NSCLC.[19]

Median OS improved with 10 months for patients receiving radiotherapy, which is in accordance with an almost 10-month improvement reported in a previous study among elderly patients.[8] This cannot be solely ascribed to the introduction of SBRT, as the risk of death for these patients was not higher in the earlier period in which SBRT was virtually unavailable. Significant improvements in OS disappear over time after adjustment for the factors in the multivariable model. In addition, patients receiving radiotherapy in period A were significantly older than those in period B. As expected, older age was associated with an increased risk of death in all treatment groups. Since SBRT was associated with a better OS than was conventional radiotherapy in multiple studies,[7, 12] the improved OS might in part be explained by the combination of SBRT and lower age of patients in period B. It would be interesting to examine in a future trial which subgroup of patients benefits the most from SBRT. The finding that in period B fewer patients received neither therapy can perhaps be ascribed to the increase in the proportion of patients receiving radiotherapy. In a study by Palma et al., the introduction of SBRT had enhanced the accessibility of curative treatment for patients with stage I NSCLC ≥75 years and reduced the number of untreated patients by 12%.[7]

A significantly higher median OS was found for surgical patients compared to those receiving radiotherapy (69 vs 29 months). Puri et al. compared surgery with SBRT in 117,618 patients with clinical stage I NSCLC. The long-term OS was significantly better in surgical patients (68 months vs 33 months, p<0.001), even in a propensity matched comparison (62 months vs 33 months, p<0.001).[20] The results from randomized control trials are inconclusive, however, and additional randomized studies should answer the question whether SBRT is a valid alternative for elderly patients with operable stage I NSCLC.[21]

The results of this study must be seen in the context of its strengths and limitations. The main strength is the large sample size and the availability of information on comorbidities, which is often lacking in other studies comparing treatment modalities.[7, 8] Furthermore, the patient population truly reflected clinical practice; it did not consist of selected, relatively fit patients, which is often the case in clinical trials. Better patient selection could have influenced the OS outcome, as surgical patients became older over time and had an increased comorbidity burden, while outcomes improved. Therefore, unidentified or unrecorded factors, such as pulmonary function and performance status probably have played a role in selecting patients for surgery. Poorer pulmonary function and performance status have been found associated with worse OS,[9, 18] and treatment choice will partially depend on these and other patient characteristics ('confounding by indication'). Patients receiving radiotherapy became younger, which probably also contributed to better outcomes. Stage migration has probably occurred due to the introduction of TNM edition 7 in 2010. This may have beneficially affected the OS rate of patients in period B, as from then on, stage I did no longer include tumours larger than 5 cm. No histopathologic proof of malignancy was obtained in 72% and 68% of patients receiving radiotherapy and neither treatment, respectively. Although these percentages are high, it reflects Dutch clinical practice. A high comorbidity burden or poor performance status may be reasons for deciding not to obtain histopathologic proof of malignancy, as well as the probability of benign disease of only 4.3% if patients met multiple criteria as described before.[16] The observational design is a limitation of this study, and causal relationships between treatment type and OS cannot be proven. Furthermore, follow-up was completed until February 2017, which implies that five-year follow-up was not complete for most of the patients diagnosed in 2012–2013. Another limitation is the fact that recurrence rates and causes of death are unknown.

In conclusion, this study provides a realistic overview of the current treatment patterns and OS among patients with stage I NSCLC in daily clinical practice in the Netherlands. The median OS improved over time for patients ≥65 years. The increased application of SBRT is promising and could be associated with improved OS and a lower proportion of patients receiving neither treatment. Surgery was still associated with the highest long-term OS and should, therefore, be preferred for relatively fit elderly patients. SBRT seems an appropriate alternative for inoperable patients.

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Chapter 4

Population-based patterns of treatment and survival for patients aged 65-74 years and ≥75 years with stage I and II non-small cell lung cancer in the Netherlands

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Abstract

Objectives Insights regarding utilization and survival of surgery and radiotherapy (stereotactic body radiotherapy (SBRT) or conventional radiotherapy (RT)) are lacking for older patients with stage I and II non-small cell lung cancer (NSCLC) in clinical practice.

Methods Data from the Netherlands Cancer Registry were retrieved for patients ≥65 years with clinical stage I-II NSCLC in 2010-2015. Descriptive analyses, overall survival (OS), and cox regression were stratified for stage I (n=8742) and II (n=3439) and compared age groups (65-74 years vs ≥75 years).

Results Patients aged 65-74 underwent surgery significantly more often compared to those aged ≥75 (stage I 55% vs 27%; stage II: 65% vs 35%), and received SBRT less often (I: 29% vs 42%; II: 5% vs 11%), conventional RT less often (I: 6% vs 11%; II 10% vs 24%) and best supportive care alone less often (BSC, I: 8% vs 19%; II: 9% vs 25%). One-year OS was significantly higher in patients aged 65-74 compared to those aged ≥75 (I: 87% vs 78%; II: 74% vs 60%); as was five-year OS (I: 49% vs 31%; II: 36% vs 18%). After adjustment for gender, histology, stage, treatment, and comorbidity, hazard ratio (HR) of death was higher for patients aged ≥75 compared to those aged 65-74 (I: HR 1.3, 95% confidence interval (CI) 1.1-1.5; II: HR 1.3 95%CI 1.1-1.7).

Conclusion Patients aged ≥75 with stage I-II NSCLC had poorer OS, underwent surgery less often, and received SBRT, conventional RT, and BSC more often than patients aged 65-74. In both stages, one-year OS within age groups was similar for surgery and SBRT. However, long-term OS adjusted for prognostic factors was superior for surgery compared to SBRT and remained poorer for those aged ≥75. Prospective research should focus on predictive characteristics for treatment selection and patient-centered outcomes.

Introduction

Non-small cell lung cancer (NSCLC) is often diagnosed in older patients, as 65% of patients are ≥65 years and one in four patients is ≥75 years.[1] For stage I and II NSCLC, surgery by video-assisted thoracic surgery (VATS) or thoracotomy is considered standard treatment among patients with potentially resectable disease. Patients who are not willing to accept surgery-related risks or who are inoperable could be offered curative radiotherapy (RT) with Stereotactic Body Radiotherapy (SBRT) or hypofractionated high-dose RT.[2, 3] Five-year relative survival rates for patients with stage I and II NSCLC ≥70 years are 54% and 32%, respectively.[4]

Surgery is associated with superior survival outcomes in clinical trials including predominantly relatively young and fit patients.[4] With the introduction of SBRT, especially older patients and high-risk surgical candidates can receive curative-intent treatment as well,[5] with local control rates of 90% after five years.[6] Recent findings indicate similar results between surgery and SBRT for operable patients.[7] Moreover, a large cohort from the National Cancer Database in the United states covering 84,839 patients with early stage NSCLC, found that the 30-day and 90-day mortality was significantly higher after surgery compared to SBRT, especially among patients aged ≥66 years.[8] Data from the Dutch Lung Surgery Audit in the Netherlands indicated that operative mortality is higher among octogenarians with NSCLC compared to patients aged 60-79 years, while the incidence of complications was similar.[9] Several factors correlate with poorer treatment tolerance and survival, such as higher age,[10] comorbidity, poorer physical performance,[9, 11] and larger extent of resection.[9, 12] Also, clinical trials state strict eligibility criteria for inclusion regarding performance status, age, and level of organ function in order to minimize the risk of complications.[13] As a result, evidence regarding outcomes of treatment is scarce for older and vulnerable patients.[12] Insights regarding treatment patterns and survival within the older adult population are highly needed in daily clinical practice. As this evidence is currently lacking, our study compares treatment patterns and overall survival (OS) for patients aged 65-74 years and those aged ≥75 years with clinical stage I and II NSCLC in daily clinical practice in the Netherlands.

Methods

All patients aged ≥65 years diagnosed with clinical stage I or II NSCLC during 2010-2015 were retrieved from the population-based Netherlands Cancer Registry, which is maintained by the Netherlands Comprehensive Cancer Organization (figure 1). Trained registrars have routinely collected data from medical records regarding patient and tumour characteristics of all newly diagnosed patients with cancer in the Netherlands since 1989 . Vital status was retrieved from the nationwide population registries network with complete follow-up until February 1st 2018. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry. The Central Committee on Research involving Human Subjects (CCMO) judged that approval of an ethics committee was not required.

The International Classification of Disease for Oncology (ICD-O3)[14] code for pulmonary tumours (C34) was used at the Netherlands Comprehensive Cancer Organization in order to include all patients with NSCLC as well as clinical diagnoses.[15] Patients with other histologies were excluded. Age (65-74 years and ≥75 years), gender, histology, and clinical stage were retrieved. Stage of disease was classified according to clinical Tumour Node Metastases (TNM) edition 7.[16] In Dutch staging guidelines, it is stated that all patients suspected for NSCLC should be staged by PET-CT scan. When the PET-CT scan is positive, lymph nodes are enlarged, and the patient is fit enough, mediastinal staging by EUS/EBUS will be applied.[2, 17] For patients without histologic confirmation of the tumour, TNM classification was registered since 2011. A small proportion diagnosed in 2010 did not have a histologic confirmation. In order to classify these patients into stage groups, trends in stage distributions between 2011-2015 were compared to those in 2010. In 2011-2015, the increase of patients with stage I NSCLC was similar to the proportion of patients without histologic confirmation in 2010. Therefore, it was decided to classify this group diagnosed in 2010 as stage I NSCLC. Information on comorbidity was available for patients in the southeastern part of the Netherlands only, covering approximately 18% of included patients. Comorbidity was registered according to a slightly adapted version of the Charlson Comorbidity Index (CCI)[18] at the Netherlands Comprehensive Cancer Organization. Retrieved comorbidity data were classified as number of comorbid conditions (0, 1, or ≥2), and type of comorbidity (respiratory, cardiovascular, digestive, hypertension, diabetes mellitus (DM), previous malignancy, or cerebrovascular accident (CVA)/hemiplegia). Treatment was categorized as VATS, thoracotomy, SBRT (3-8 fractions), conventional RT, chemotherapy, chemoradiotherapy (chemotherapy and radiotherapy within 90 days of each other), and Best Supportive Care (BSC).

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 24.0. All analyses were stratified for stage of disease (I and II) and age groups. Descriptive statistics and OS were compared between age groups (65-74 years and ≥75 years) and differences were assessed for significance by the X^2-test for categorical variables and the Mann-whitney U test for continuous variables ($P<0.05$ two sided). Results were displayed as number (percentage) or median (interquartile range (IQR)). As chemotherapy and chemoradiotherapy

covered only small proportions and are not considered regular treatment options for stage I-II NSCLC,[2] these were excluded from survival analyses. OS rates were calculated from the date of diagnosis until death or until February 1st 2018 by median, one-year, and five-year OS, and were visualised by the Kaplan-Meier method. Median follow-up was estimated with the reverse Kaplan-Meier method.[19] Hazard Ratios (HRs) for mortality were calculated by Cox proportional hazard regression analyses. HRs were adjusted for factors affecting survival based on previous studies and included in model 1: utilized treatment,[7] gender,[20] age,[4, 9, 10] stage,[21] and histology[22]. In subanalyses, the cohort of the southeastern part of the Netherlands was used to investigate whether number of comorbid conditions[23] was an independent predictive factor for mortality as well, and was added in model 2. Imputation of missing values for comorbidity was not performed for patients outside the southeastern part of the Netherlands, as approximately 80% of outcomes would be imputed. Both OS rates and HRs were displayed with corresponding 95% confidence intervals (95%CI). HR > 1.0 indicates an increased hazard of death. The HR was considered statistically significant when the 95%CI was completely above or below 1.0.

Results

In the Netherlands, 12,182 patients aged ≥65 years were diagnosed with stage I-II NSCLC between 2010 and 2015 (figure 1), covering 19% of all primary cases of lung cancer. Over half of the study population was aged 65-74 years (53%, table 1). For stage I NSCLC, patients aged 65-74 years underwent VATS (32% vs 16%) and thoracotomy (23% vs 11%) significantly more often, while SBRT (29% vs 42%), conventional RT (6% vs 11%), and BSC (8% vs 19%) were utilized significantly less often compared to those aged ≥75 years. Two or more comorbid conditions were less often present among patients aged 65-74 years (66%) compared to those aged ≥75 years (73%), whereas 26% and 23% suffered from one comorbid condition, respectively. Patients aged ≥75 years suffered more often from DM (p=0.001), previous malignancy (p=0.02), and CVA or hemiplegia (p=0.004) compared to patients aged 65-74 years. For stage II NSCLC, patients aged 65-74 years underwent VATS significantly more often (25% vs 13%), as well as thoracotomy (40% vs 22%), and chemoradiotherapy (9% vs 5%), while SBRT (5% vs 11%), conventional RT (10% vs 24%), and BSC (9% vs 25%) were utilized significantly less often compared to those aged ≥75 years. Proportions of the number and type of comorbid conditions were comparable between age groups.

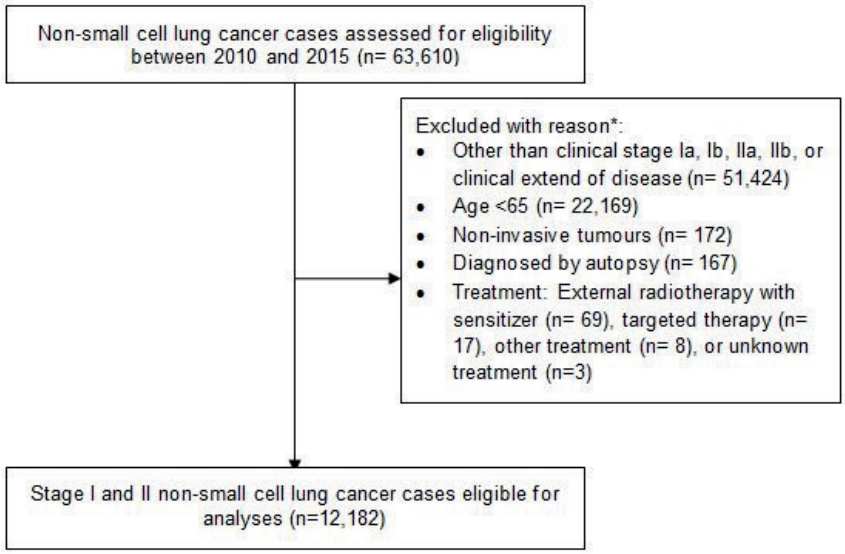


Figure 1. Flow chart of eligible patients ≥65 years with stage I and II non-small cell lung cancer (2010- 2015) * Characteristics of all excluded patients. Multiple characteristics could be applicable to one patient. Therefore, the exclusion numbers cannot be deducted from the total number of non-small cell lung cancer cases in order to calculate the total number of eligible cases

Median follow-up was 58 months (95%CI 57-59 months). Figure 2a and 2b display that within age and stage groups, OS seemed similar until one year for VATS, thoracotomy, and SBRT. However, survival curves were declining more rapidly after one year among those aged ≥75. After two years, both surgical approaches indicated superior OS compared to SBRT and conventional RT among patients aged 65-74 years for both stages, and among those aged ≥75 years for stage I NSCLC only. Furthermore, SBRT showed superior OS compared to conventional RT. For patients aged ≥75 specifically, VATS showed superior survival after two years in both stages as compared to other treatment options. For stage I, this is consecutively followed by thoracotomy and SBRT. For those aged ≥75 years with stage II NSCLC, OS was similar up until two years for VATS and SBRT and superior with respect to other treatment options, while OS for SBRT and thoracotomy were similar and lower compared to VATS after 3 years.

One-year and five-year OS rates were displayed in table 2. For stage I NSCLC, these OS rates were significantly higher for patients aged 65-74 years (87% and 49%, respectively) compared to those aged ≥75 years (78% and 31%, respectively). After stratification of treatment, both one-year and five-year OS rates were significantly higher for patients aged 65-74 years compared to those aged ≥75 years for all treatments. However, one-year OS was comparable between age groups for conventional RT and five-year OS were comparable for both conventional RT and SBRT. For stage II NSCLC, one-year and five-year OS rates were significantly higher for patients aged 65-74 years (74% and 36%, respectively) compared to those aged ≥75 years (60% and 18%, respectively, table 2). After stratification of treatment, one-year OS was comparable between age groups for all treatment options. The five-year OS rates were significantly different between age groups for thoracotomy (46% vs 29%) and SBRT (33% vs 27%), but were comparable for all other treatment options.

The adjusted HR of death are displayed in table 3. Patients aged ≥75 showed a significant 1.3-fold higher HR of death compared to those aged 65-74 years for both stages (model 2 (including comorbidity as well)). The HR of death was also significantly higher for SBRT (stage I: HR 1.9 (95%CI 1.5-2.3); stage II: HR 2.5 (95%CI 1.6-3.8)) and conventional RT (stage I: HR 2.6 (95%CI 2.0-3.4); stage II: HR 2.8 (95%CI 2.0-3.9)) compared to VATS, and the highest HR of death was seen for BSC (stage I: HR 4.2 (95%CI 3.3-5.3); stage II: HR 7.2 (95%CI 5.1-10)). For patients with stage I NSCLC, females showed a significantly decreased HR of death compared to males (HR 0.79 (95%CI 0.68-0.91)). A significant higher HR of death was seen for patients with stage IB (HR 1.5 (95%CI 1.3-1.7)) compared to stage IA, and for ≥2 comorbid conditions (HR 1.5 (95%CI 1.1-2.1)) compared to no comorbid conditions. For patients with stage II NSCLC, stage IIB was associated with significantly decreased HR of death compared to stage IIA (HR 0.71 (95%CI 0.58-0.86)).

Table 1. Overview of patient and tumour characteristics of older patients with stage I-II non-small cell lung cancer (2010-2015) according to stage and age groups

Stage		**I**			**II**	
Age years	**65-74**	**≥75**	**P-value**	**65-74**	**≥75**	**P-value**
Total n (%)	4694 (54)	4048 (46)		1774 (52)	1665 (49)	
Median age years *(IQR)*	69 (67-72)	79 (77-82)	<0.01*	69 (67-72)	79 (77-83)	<0.01*
Gender Male %	59	65	<0.01*	66	75	<0.01*
Histology %			<0.01*			<0.01*
Squamous CC	31	27		48	51	
Adenocarcinoma	41	27		36	22	
NOS/ large CC	28	46		17	27	
Stage %			0.01*			0.30
A	68	66		46	48	
B	32	34		54	52	
Treatment %			<0.01*			<0.01*
VATS	32	16		25	13	
Thoracotomy	23	11		40	22	
SBRT	29	42		5	11	
Conventional RT	6	11		10	24	
Chemotherapy	1	0,5		3	2	
Chemoradiotherapy	1	0,5		9	5	
BSC	8	19		9	25	
Comorbidity**						
Available n (%)	866 (18)	709 (18)		332 (19)	300 (18)	
Number %			0.002*			0.42
0	8	4		13	10	
1	26	23		24	23	
≥2	66	73		63	67	
Type %						
Respiratory	45	41	0.06	34	34	0.99
Cardiovascular	51	58	0.06	50	54	0.24
Hypertension	36	38	0.55	34	41	0.08
DM	14	21	0.001	15	19	0.15
Previous malignancy	36	42	0.02	28	29	0.92
CVA/hemiplegia	5	8	0.004	9	12	0.28
Digestive	8	9	0.76	9	7	0.27

Abbreviations: *n* 'Number' IQR 'InterQuartile Range', CC 'cell carcinoma', VATS 'Video Assisted Thoracic Surgery', SBRT 'Stereotactic Body Radiotherapy', RT 'Radiotherapy', BSC 'best supportive care', CVA 'Cerebrovascular accident', DM 'Diabetes Mellitus'. * indicates significant differences between age groups. **Subanalyses of 2207 patients (18%) with available information on comorbidity

Table 2. Overall survival rates and median overall survival of older patients with stage I-II non-small cell lung cancer (2010-2015) according to stage, age groups, and treatment

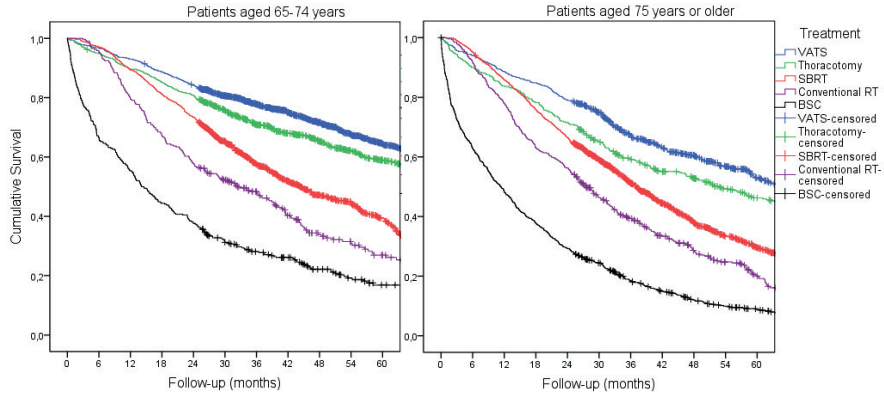
Stage	**I**		**II**	
1-year OS % (95%CI)	87 (86-88)*	78 (77-79)*	74 (72-76)*	60 (57-62)*
Treatment				
VATS	93 (92-94)*	89 (86-91)*	85 (81-88)	80 (75-86)
Thoracotomy	90 (88-91)*	84 (80-87)*	81 (78-84)	76 (72-80)
SBRT	89 (88-91)*	86 (84-87)*	80 (72-89)	82 (76-87)
Conventional RT	79 (75-84)	78 (74-82)	66 (59-73)	57 (52-62)
BSC	55 (50-61)*	45 (42-49)*	18 (12-24)	25 (22-30)
5-year OS % (95%CI)	49 (48-51)*	31 (29-32)*	36 (34-39)*	18 (16-20)*
Treatment				
VATS	64 (62-67)*	53 (49-58)*	45 (39-50)	43 (36-51)
Thoracotomy	59 (56-62)*	46 (42-51)*	46 (42-50)*	29 (24-34)*
SBRT	40 (36-43)*	30 (27-33)*	33 (22-45)	27 (19-36)
Conventional RT	27 (21-33)	20 (16-25)	14 (8.2-21)	6.7 (3.7-9.6)
BSC	17 (12-21)*	8.8 (6.5-11)*	3.8 (0.7-6.9)	2.3 (0.7-3.9)
Median OS months (95%CI)	60 (57-63)*	33 (32-35)*	35 (31-38)*	17 (15-18)*
Treatment				
VATS	83 (76-91)*	65 (57-73)*	52 (43-61)	43 (31-56)
Thoracotomy	82 (75-90)*	53 (42-64)*	50 (42-58)*	29 (24-34)*
SBRT	44 (40-48)*	37 (35-39)*	29 (19-39)	30 (26-35)
Conventional RT	32 (25-39)	28 (24-31)	16 (13-20)	14 (12-15)
BSC	14 (12-17)	11 (9.8-13)	34 (2.1-4.7)	5.3 (4.3-6.3)

Abbreviations: 95%CI '95 percent Confidence Interval', OS 'Overall Survival', VATS 'Video Assisted Thoracic Surgery', SBRT 'Stereotactic Body Radiotherapy', RT 'radiotherapy', BSC 'best supportive care'. * indicates significant differences when confidence intervals between age groups are not overlapping

Table 3. Multivariable cox proportional hazard ratios of older patients diagnosed with stage I-II non-small cell lung cancer (2010-2015) according to stage

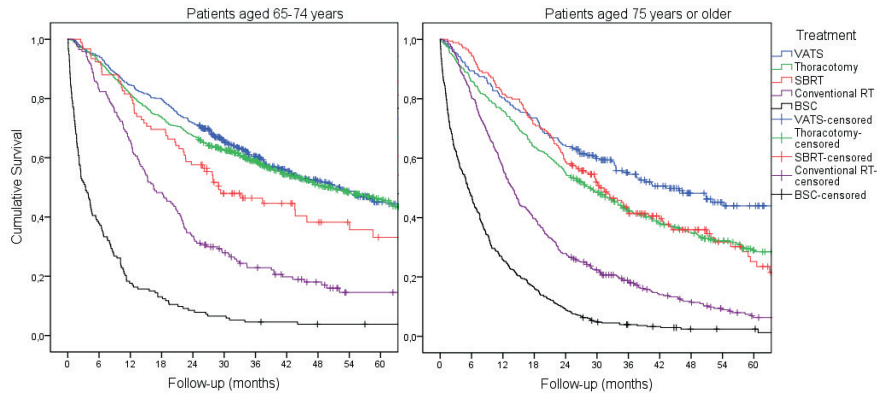
Stage		**I**		**II**	
Model 1		**HR (95%CI)**	**P-value**	**HR (95%CI)**	**P-value**
Age	65-74 years	Reference		Reference	
	≥75 years	1.3 (1.2-1.3)	<0.01	1.1 (0.99-1.3)	<0.01
Gender	Male	Reference		Reference	
	Female	0.79 (0.75-0.84)	<0.01	0.86 (0.78-0.94)	<0.01
Histology	Squamous CC	Reference		Reference	
	Adenocarcinoma	0.86 (0.79-0.92)	<0.01	0.92 (0.83-1.0)	0.11
	NOS/large CC	1.0 (0.97-1.1)	0.23	1.0 (0.91-1.1)	0.78
Stage	A	Reference		Reference	
	B	1.5 (1.4-1.6)	<0.01	0.78 (0.72-0.86)	<0.01
Treatment	VATS	Reference		Reference	
	Thoracotomy	1.1 (0.98-1.2)	0.13	1.3 (1.1-1.6)	0.06
	SBRT	1.9 (1.7-2.1)	<0.01	1.3 (1.1-1.6)	0.01
	Conventional RT	2.4 (2.2-2.7)	<0.01	2.7 (2.3-3.2)	<0.01
	BSC	5.0 (4.5-5.5)	<0.01	6.6 (5.7-7.7)	<0.01
Model 2 *					
Age	65-74 years	Reference		Reference	
	≥75 years	1.3 (1.1-1.5)	<0.01	1.3 (1.1-1.7)	0.01
Gender	Male	Reference		Reference	
	Female	0.79 (0.68-0.91)	<0.01	0.92 (0.73-1.2)	0.49
Histology	Squamous CC	Reference		Reference	
	Adenocarcinoma	0.93 (0.78-1.1)	0.41	1.1 (0.88-1.5)	0.35
	NOS/large CC	1.1 (0.91-1.3)	0.29	1.1 (0.86-1.4)	0.46
Stage	A	Reference		Reference	
	B	1.5 (1.3-1.7)	<0.01	0.71 (0.58-0.86)	<0.01
Treatment	VATS	Reference		Reference	
	Thoracotomy	1.2 (0.92-1.5)	0.23	0.995 (0.74-1.3)	0.98
	SBRT	1.9 (1.5-2.3)	<0.01	2.5 (1.6-3.8)	<0.01
	Conventional RT	2.6 (2.0-3.4)	<0.01	2.8 (2.0-3.9)	<0.01
	BSC	4.2 (3.3-5.3)	<0.01	7.2 (5.1-10)	<0.01
Number of comorbid conditions	0	Reference		Reference	
	1	1.3 (0.93-1.8)	0.13	0.92 (0.64-1.3)	0.64
	≥2	1.5 (1.1-2.1)	0.01	0.93 (0.68-1.3)	0.66

Abbreviations: HR 'Hazard Ratio', 95%CI '95% Confidence Interval', VATS 'Video Assisted Thoracic Surgery', SBRT 'Stereotactic Body Radiotherapy', RT 'Radiotherapy', BSC 'best supportive care', CC 'Cell Carcinoma', NOS 'Not Otherwise Specified'. *Subanalyses of 2207 patients (18%) with available information on comorbidity



Number at risk												
VATS	1596	1482	1335	971	661	379	703	624	559	395	286	173
Thoracotomy	1089	975	879	673	525	398	432	362	309	238	195	146
SBRT	1340	1197	984	581	338	188	1709	1466	1135	688	379	205
Conventional RT	292	232	169	112	61	37	446	348	251	151	91	46
BSC	280	128	75	43	25	8	707	322	181	91	45	22

Figure 2a. Kaplan-Meier survival curves of older patients with stage I non-small cell lung cancer (2010-2015) according to age groups and treatment including the number of patients at risk (VATS 'Video Assisted Thoracic Surgery', SBRT 'Stereotactic Body Radiotherapy', RT 'Radiotherapy', BSC 'best supportive care')



Number at risk												
VATS	445	376	319	205	128	69	211	170	137	88	50	30
Thoracotomy	703	572	474	349	246	178	362	275	199	130	99	58
SBRT	92	74	53	26	18	12	179	146	105	56	32	15
Conventional RT	170	112	57	31	18	8	391	222	109	57	31	11
BSC	149	24	10	6	4	3	409	103	35	11	4	3

Figure 2b. Kaplan-Meier survival curves of older patients with stage II non-small cell lung cancer (2010-2015) according to age groups and treatment including the number of patients at risk (VATS 'Video Assisted Thoracic Surgery', SBRT 'Stereotactic Body Radiotherapy', RT 'Radiotherapy', BSC 'best supportive care')

Discussion

Evidence regarding treatment options and outcomes are scarce for older patients with NSCLC and evidence-based insights are highly needed for this vulnerable population. The aim of this study was to compare treatment patterns and OS between patients aged 65-74 years and those aged ≥75 years with clinical stage I and II NSCLC in daily clinical practice. Patients aged ≥75 years underwent surgery less often, and received SBRT, conventional RT, and BSC more often than patients aged 65-74 years in both stages. Superior one-year OS was seen for VATS, thoracotomy, and SBRT among patients aged 65-74 years compared to those aged ≥75 years with stage I NSCLC. However, one-year OS was similar between those treatment options and both age groups among patients with stage II NSCLC. Superior long-term OS was seen for VATS and thoracotomy among both age groups with stage I NSCLC and among those aged 65-74 years with stage II NSCLC. However, superior long-term OS for patients aged ≥75 years with stage II NSCLC was found after VATS. After adjustment for known prognostic factors including comorbidity, the HR of death remained significantly higher for patients aged ≥75 years compared to their younger counterparts in both stage groups.

The current study found that older patients with NSCLC undergo surgery less often compared to younger patients.[5] Recently, improvements in survival after both surgery and RT have been found.[5, 24] While SBRT is recommended for inoperable patients over non-SBRT radiotherapy techniques,[2, 25] the superiority of surgical resection over SBRT is debated for operable and older patients.[7, 26] In our study, similar one-year OS rates were found for VATS and SBRT within age groups. Comparable short-term survival outcomes for surgery and RT were also found in a retrospective multicenter cohort,[27], a large registration database,[8] clinical trials including operable patients,[7] and a meta-analysis.[28] However, long-term OS in our study was superior for VATS and thoracotomy among patients aged 65-74 years in both stages and for those aged ≥75 years with stage II, whereas only VATS was superior for those aged ≥75 years with stage II NSCLC. SBRT was associated with better OS compared to conventional RT in both age groups, which was also found in a meta-analysis without age-restrictions.[25] Although the adjusted HR of death for both conventional RT and SBRT were increased compared to VATS, this increase was higher for conventional RT than SBRT in our study. SBRT could be a treatment option for older adults with stage I NSCLC, as local control rates of >90% can be achieved after five years,[6] and treatment tolerance is acceptable.[29] Moreover, the safety and effectiveness of SBRT for patients aged ≥80 years was previously demonstrated,[30] and comparable short term survival rates were previously found for surgery and radiotherapy among patients aged ≥85 years,[31] which are partially represented in our dataset as well. A small proportion of patients with stage II NSCLC received SBRT. Although this treatment is not standard for stage II disease, it could be an option for specific situations and is administered to patients with tumours >5cm in the Netherlands.[32] Although, short-term OS after SBRT within age and stage groups seemed comparable to VATS in our study, long-term outcomes remain to be in favor of surgery in both older age groups. However, SBRT should not be withheld from older patients based on stage alone and it should be kept in mind that surgical patients with long-term survival are a selected subpopulation among older patients with NSCLC and are more likely to be included in clinical trials.

Explanations for poorer OS in older patients are diverse and could depend on a combination of age ≥75 years,[10,33] short life expectancy,[34] (undiagnosed or unforeseen) lymph node metastases,[35] poorer physical performance,[9, 11] and comorbid conditions.[2, 9] It was expected that pulmonary comorbid conditions would be different between age groups, impacting treatment choice among the oldest group and negatively impacting OS.[9, 36, 37] Differences in OS between treatment groups were significant, and it is expected that younger and fitter patients were selected for surgery compared to radiotherapy in both stages.[2] Although we were able to adjust the HR of death for the number of comorbid conditions, adjustment was not optimal as severity of comorbidity was not available. Treatment decisions could also depend on other prognostic factors than those accounted for in this study, such as performance status, cognitive status, pulmonary function, and preferences of the patient.[10] Patient involvement in treatment decision-making is important as almost half of patients with stage I-II NSCLC experience conflicts in treatment decision-making, and one in three patients feel uninformed.[38] This implies that not only patient or tumour characteristics should be taken into account to determine which treatment is the most optimal for each older individual, but patient-centered outcomes should be taken into account as well.[39] A recent study found that health utility, or summarized quality of life, was not significantly different between patients receiving surgery or SBRT for stage I NSCLC.[40] Insights regarding treatment patterns and OS in daily clinical practice would be even more valuable when associated with patient preferences and patient-centered outcomes.[38] This information could improve the treatment decision-making process for both patients and physicians and outcomes for the heterogeneous group of older patients with stage I and II NSCLC.

Strengths of this population-based study were the nationwide coverage and inclusion of unselected patients with clinical stage I-II NSCLC between 2010 and 2015 in the Netherlands. This leads to more generalized results compared to other studies including institutional data. Other strengths were the high quality standard of included data, the completeness regarding obtained treatment, and the availability of information on comorbidity in the southeastern part of the Netherlands. Furthermore, all citizens in the Netherlands have equal access and imbursement to healthcare. Altogether, this leads to the selection of (almost) all patients in the given period, and a description of treatment and survival which is not influenced by financial resources. However, some limitations should be mentioned. As this is an observational study, causal relations cannot be drawn. Dutch practice guidelines indicate that patients who present with a high-risk profile of lung cancer are suspected of stage I NSCLC based on a new or growing [18] FDG-PET positive lesion. These patients are diagnosed with a primary (stage I) lung tumour.[41] Information regarding treatment choice, performance status, radiation dose, hospitalization, completion of treatment, pulmonary function, and adverse events was unavailable. Information on comorbidity was known for 18% of patients. Nevertheless, valuable insights have been gained regarding treatment, OS, and adjusted risks of death for both older age groups and stages. Despite a median follow-up of 58 months, five-year OS rates could have been slightly higher if a longer follow-up period could have been taken into account. The fairly large difference in OS between SBRT and conventional RT could be explained by some patients receiving palliative doses of conventional RT. Unfortunately, information on palliative or curative doses was not available. Also,

some tumours can only be treated with SBRT due to the location and risk of surgery related complications. Furthermore, confounding by indication should be considered, as treatment choice in clinical practice partially depends on patient characteristics such as comorbid conditions. Also, therapeutic nihilism is of significant importance for the interpretation of treatment patterns and outcomes among older patients, as it can be thought that (standard) treatment would be more harmful than beneficial.

Since clinical trials including older patients often suffer from slow accrual and restrictions regarding age, performance and cognitive status and comorbid conditions, large nation-wide cohort studies including big data collection including treatment selection, and patient centered outcomes can help with generalizability and treatment decision making.[42] Also, wishes and expectations of both patients and caregivers should have a more prominent role in the treatment-decision process to gain the most optimal and personal treatment decision.[38, 43] Altogether, evidence can be gained for the heterogeneous population with often vulnerable and frail older patients who are not always fit for surgery, in the light of the best evidence, clinician's expertise, and preferences of patients and caregivers.

Conclusion

Patients aged ≥75 years with stage I and II NSCLC underwent surgery less often than those aged 65-74 years and had poorer OS, even after adjustment for other known prognostic factors. In both stages, one-year OS within age groups was similar for surgery and SBRT. However, adjusted long-term OS was superior for surgery compared to SBRT and remained poorer for those aged ≥75. These findings could form the basis for impactful trials as older patients cannot be compared based on age alone. The perspectives regarding treatment and survival for this heterogeneous and vulnerable group of older patients with stage I-II NSCLC should be optimized by prospective research focusing on predictive patient characteristics for treatment selection and patient-centered outcomes such as complications and quality of life with respect to survival.

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5

Chapter 5

Patterns of treatment and survival among older patients with stage III non-small cell lung cancer

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Abstract

Introduction Patterns of treatment and survival are largely unknown for older patients with stage III non-small cell lung cancer (NSCLC) in daily clinical practice.

Methods All patients ≥65 years with stage III NSCLC (2009-2013) were included from the population-based Netherlands Cancer Registry. Descriptive and multivariable treatment and survival analyses were stratified for patients aged 65-74 years and ≥75 years.

Results Compared to older patients (n=3,163), those aged 65-74 years (n=3,876) underwent more often surgery (21% vs 12% for stage IIIA), chemoradiotherapy (47% vs 22% for both stage IIIA and IIIB), and chemotherapy (23% vs 12% for stage IIIB), and received less radiotherapy (8% vs 22% for both stage IIIA and IIIB). One-year survival was significantly higher among patients aged 65-74 compared to those aged ≥75 (61% vs 43%, for stage IIIA and 45% vs 30% for stage IIIB; P<0.01). However, stratification of treatment showed similar survival rates between age groups. Among patients aged 65-74 years, the multivariably adjusted hazard ratio (HR) of death was twice as high for patients receiving radiotherapy (HR 1.9 (95%CI 1.6-2.2) for stage IIIA and HR 2.5 (95%CI 2.1-3.0) for stage IIIB) and chemotherapy (HR 2.2 (95%CI 1.9-2.5) and HR 2.2 (95%CI 1.8-2.7), respectively) compared to chemoradiotherapy, and were slightly lower for patients aged ≥75 years receiving radiotherapy (HR 1.6 (95%CI 1.4-1.9) and HR 1.8 (95%CI 1.5-2.1), respectively) and chemotherapy (HR 2.2 (95%CI 1.8-2.7) and HR 1.8 (95%CI 1.5-2.2), respectively). Comorbidity was not significantly associated with poorer survival (p=0.07).

Conclusion Chemoradiotherapy was more often applied among patients aged 65-74 years compared to those aged ≥75. While survival was worse for patients aged ≥75 years, differences between age groups largely disappeared after stratification for treatment. Future research should focus on predictive patient characteristics to distinguish patients within the heterogeneous older population who can benefit from curative-intent treatment.

Introduction

Half of patients with non-small cell lung cancer (NSCLC) are aged 65 years or older at the time of diagnosis, whereas one in four is aged 75 years or older in the Netherlands.[1] Overall 5-year survival remains below 15% for patients with stage III NSCLC in daily clinical practice.[2] Concurrent chemoradiotherapy is considered standard treatment for patients with unresectable stage III NSCLC, as it results in a survival benefit of 5,7% at 3 years and 4,5% at 5 years compared to sequential chemoradiotherapy according to clinical trials.[3-5] In case of resectable stage IIIA NSCLC, surgery with adjuvant chemotherapy is considered standard treatment.[3, 5] Older and frail patients are often excluded from clinical trials as strict eligibility criteria such as performance status, age, and strict levels of organ function are retained in order to minimize the risk of complications.[6] Elderly patients with NSCLC receive standard treatment less often.[7-9] This could be explained by a lack of evidence to extrapolate treatment guidelines to older and vulnerable patients in everyday clinical practice. Despite this lack of evidence, modest increases in the application of chemoradiotherapy were seen for older patients over time in the Netherlands.[2] A recent retrospective study from our group indicated that survival among patients with unresectable stage III NSCLC ≥70 years in the southeastern part of the Netherlands was not significantly superior for those who received concurrent chemoradiotherapy as compared to sequential chemoradiotherapy and even radiotherapy alone. Also, severe comorbidity was associated with worse treatment tolerance and worse survival in case of concurrent and sequential chemoradiotherapy.[10] Therefore, it is important to assess patterns of treatment and survival in this heterogenous and older population in order to distinguish patient groups for optimal treatment strategies by patient and tumour characteristics.

The aim of this population-based study was to describe unselected patients with stage III NSCLC aged 65-74 years and those aged ≥75 years regarding patterns of treatment and survival in relation with patient and tumour characteristics in the Netherlands.

Methods

All patients diagnosed with stage III NSCLC during 2009-2013 who were aged 65 years or older were retrieved from the population-based Netherlands Cancer Registry. Patients diagnosed by autopsy were not included. Since 1989, trained registrars routinely collect data from medical records regarding patient and tumour characteristics of all newly diagnosed cancer patients in the Netherlands. These data are >95% complete and have national coverage. Vital status was retrieved from the nationwide population registries network (follow-up until February 1st 2017). This study was approved by the Privacy Review Board of the Netherlands Cancer Registry. The Central Committee on Research involving Human Subjects (CCMO) judged that approval from an ethics committee was not required.

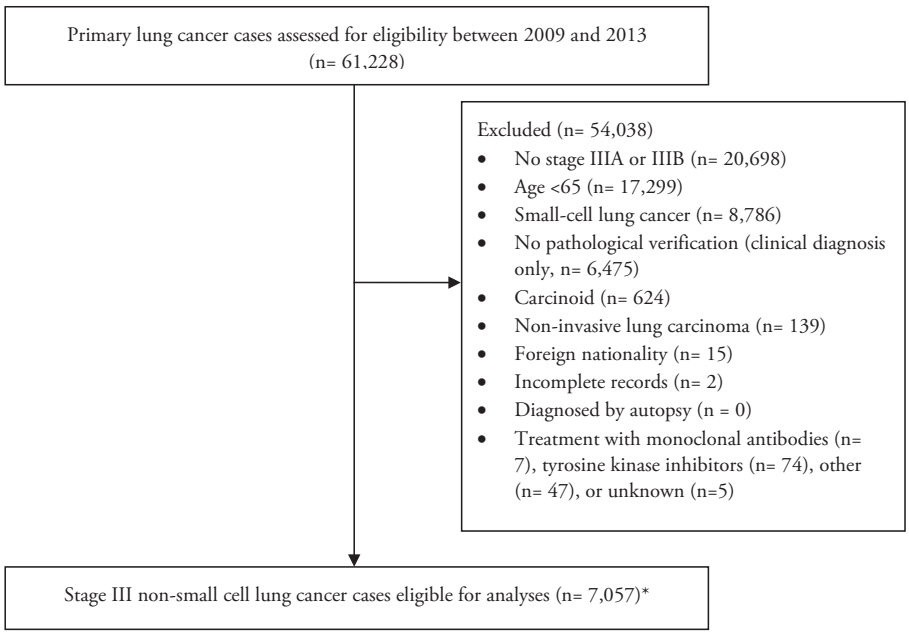
The International Classification of Disease for Oncology (ICD-O3)[11, 12] was used to code topography (C34) and morphology (invasive 8010-8020, 8022-8035, 8046-8230, 8243-8246, 8250-8576, 8972, 8980-8982, and 9110).[13] Diagnoses of other

histologies or no pathological verfication were excluded (figure 1). Stage of disease was classified according to pathological Tumour Node Metastases (TNM) supplemented with clinical TNM (edition 6 up to 2009, edition 7 from 2010 onwards).[14] The patient population was described according to two age groups (65-74 years and ≥75 years). Gender, histology (adenocarcinoma, squamous cell carcinoma, large cell carcinoma and other NSCLC[13]), and stage (IIIA and IIIB) were included in analyses. Information on comorbidity was available for patients in the southeastern part of the Netherlands only, covering approximately 15% of the Dutch population. Comorbidity was registered according to a slightly adapted version of the Charlson Comorbidity score[15]: it was classified as number of comorbid conditions (0, 1, or ≥2), and type of comorbidity (respiratory, cardiovascular, hypertension, diabetes, previous malignancy, digestive or CVA/hemiplegia). Obtained primary treatment was categorized as surgery (including (neo)adjuvant therapy (if applicable) for stage IIIA), chemoradiotherapy (including radiotherapy with sensitizer, chemotherapy followed by radiotherapy), radiotherapy alone (both curative-intent and palliative), chemotherapy alone, and Best Supportive Care (BSC). When the time interval between treatments was available, concurrent chemoradiotherapy (<30 days between dates of start of both chemotherapy and radiotherapy) and sequential chemoradiotherapy (>30 days between chemotherapy and radiotherapy) could be distinguished. However, time between treatments was unspecified in 22% of patients receiving chemoradiotherapy. Subanalyses were not performed for concurrent and sequential chemoradiotherapy as a large proportion of those receiving chemoradiotherapy could not be categorized. Overall survival (OS) was calculated from the time of diagnosis until death or until February 1st 2017, including median, 1-year, and 3-year OS rate.

Statistical analyses

All analyses were performed using IBM SPSS Statistics 22.0. Stratification according to stage was consistently applied as available treatment options and prognoses differ for those with stage IIIA and IIIB NSCLC. Patient and tumour characteristics were described according to age groups, and statistical significant differences (P<0.05 two sided) were determined by the X^2-test for categorical variables and the Mann-whitney U test for medians of continuous variables. OS rates were calculated for each age group, stage, and obtained treatment. OS was depicted by estimates of the Kaplan-Meier method and significant differences between treatment groups were determined by the log-rank test (P<0.05). Median follow-up was estimated with the reverse Kaplan-Meier method.16 Hazard Ratios (HRs) for mortality were calculated by Cox proportional hazard regression analyses and described according to age groups. HR>1.0 indicated increased hazard of death. Descriptive factors were selected according to the backward stepwise likelihood ratio method and were excluded if P>0.10. The HR was adjusted for treatment, gender, age, and histology for all included patients. In addition, the cohort of the southeastern part of the Netherlands was used to investigate whether comorbidity was an important and independent predictive factor for survival. Imputation of missing values for comorbidity was not performed for patients outside the southeastern part of the Netherlands, as approximately 80% of outcomes would be imputed. Both OS rates and HRs were displayed with corresponding 95% confidence intervals (95%CI). The HR was considered statistically significant when the 95%CI was completely above or below 1.0.

Figure 1. Flow chart of eligible older patients diagnosed with stage III non-small cell lung cancer (2009- 2013)



* This number can slightly deviate from the finally included number of cases as some cases could be added or excluded from the database after initial data retrieval for this study

Results

In the Netherlands, 7,039 patients aged 65 years or older were diagnosed with stage III NSCLC between 2009 and 2013 (Table 1). This population covers 11% of all primary lung cancer cases in the Netherlands between 2009 and 2013, and 29% of patients diagnosed with stage III NSCLC (figure 1).

Table 1. Overview of patient and tumour characteristics of older patients diagnosed with stage III non-small cell lung cancer (2009-2013) according to stage and age groups

Stage		**IIIA**			**IIIB**	
Age yrs	**65-74**	**≥75**	**P-value**	**65-74**	**≥75**	**P-value**
Total N (%)	2160 (55)	1800 (45)		1716 (56)	1363 (44)	
Median age yrs (IQR)	69 (67-72)	79 (77-82)	0.00	69 (67-72)	79 (77-82)	0.00
Gender Male %	67	75	0.00	69	73	0.04
Histology %						
Squamous CC	46	52	*0.00*	42	44	*0.00*
Adenocarcinoma	34	27		35	28	
NOS/ large CC	20	21		23	28	
Treatment * %						
Surgery	21	12	*0.00*	-	-	*0.00*
Chemoradiotherapy	47	24		47	20	
Radiotherapy	8	23		8	22	
Chemotherapy	11	8		23	12	
BSC	13	33		21	46	
Comorbidity**						
Available N (%)	392 (57)	290 (43)		325 (58)	234 (42)	
Number %						
0	16	10	*0.03*	17	12	0.06
1	26	23		29	24	
≥2	58	67		55	64	
Type %						
Respiratory	35	38	0.46	35	32	0.50
Cardiovascular	47	58	*0.00*	44	58	*0.00*
Hypertension	35	39	0.28	30	32	0.60
DM	18	24	0.06	13	18	0.16
Previous malignancy	22	29	0.05	21	25	0.28
CVA/hemiplegia						
Digestive	7	7	0.97	6	6	0.94
	6	9	0.21	7	12	0.07

Abbreviations: yrs 'years', *N 'Number'* IQR 'InterQuartile Range', CC 'cell carcinoma', BSC 'Best Supportive Care', CVA 'Cerebrovascular accident', DM 'Diabetes Mellitus'. P<0.05 is considered statistically significant. *Treatment options: surgery (with and without (neo)adjuvant chemotherapy, adjuvant (stereotactic) radiotherapy, or adjuvant radiotherapy with sensitizer); chemoradiotherapy (with and without adjuvant surgery); (stereotactic) radiotherapy; chemotherapy (with and without adjuvant chemotherapy, palliative radiotherapy, monoclonal antibodies, or tyrosine kinase inhibitors); best supportive care. As surgery is unconventional in clinically staged IIIB NSCLC, these numbers and percentages are not displayed. **Subanalyses of 1241 patients (18%) with available information on comorbidity

Almost half of the study population was ≥75 years old (45% of stage IIIA and 44% of stage IIIB, Table 1). The proportion of patients with stage IIIA receiving chemoradiotherapy was significantly higher for those aged 65-74 years (47%) compared to those aged ≥75 years (24%). The same pattern was observed for surgery (21% vs 12%, respectively). Radiotherapy alone and BSC were offered significantly less often for those aged 65-74

years compared to patients aged ≥75 years (8% vs 23% for radiotherapy and 13% vs 33% for BSC), while the administration of chemotherapy alone was comparable (11% vs 8%). For stage IIIB, both age groups showed comparable proportions of chemoradiotherapy and radiotherapy alone as those with stage IIIA. However, chemotherapy alone was applied more often among patients aged 65-74 years (23%) compared to those aged ≥75 years (12%), while patients aged ≥75 years received more BSC (46%) than those aged 65-74 years (21%). Information on comorbidity was available in 18% of patients. In both stages, cardiovascular comorbidity was significantly more present among those aged 75 years or older (58% for both stage IIIA and IIIB) compared to those aged 65-74 years (47% for stage IIIA and 44% for stage IIIB). Two or more comorbid conditions were significantly more present among those with stage IIIA aged ≥75 years (67%) compared to those aged 65-74 years (58%).

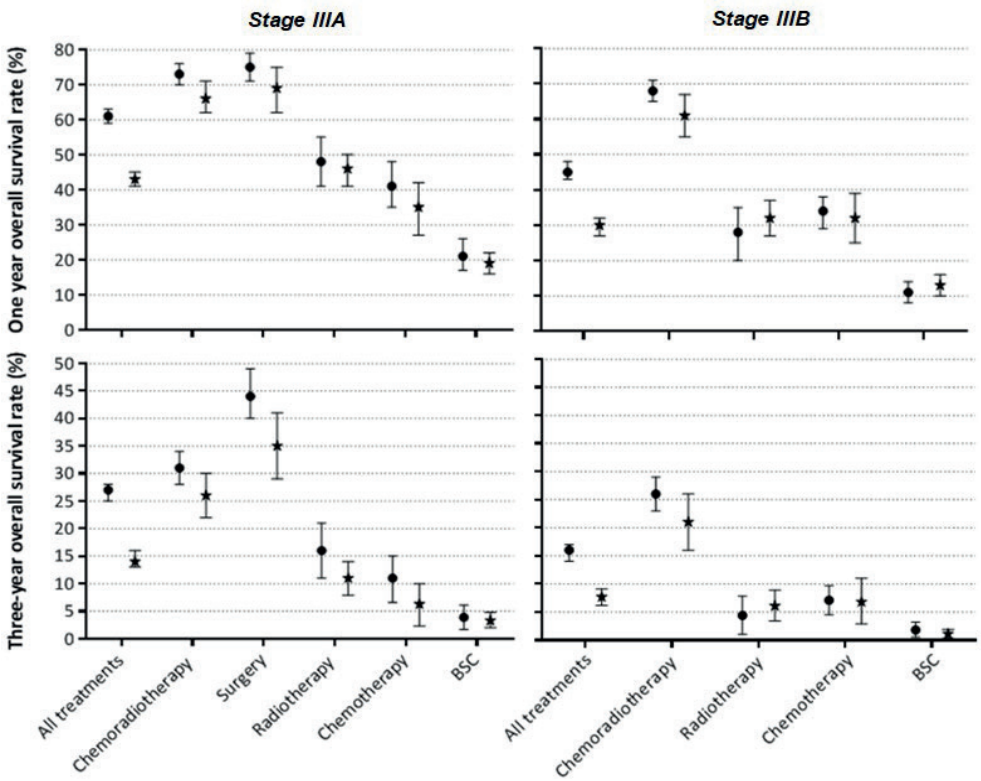


Figure 2. One-year and three-year overall survival rates with 95% confidence intervals of older patients diagnosed with stage III non-small cell lung cancer (2009-2013) according to obtained treatment, stage, and age groups (• displays patients aged 65-74 years, *displays patients aged ≥75 years, BSC 'best supportive care')

Median OS, as well as 1-year, and 3-year OS were significantly higher for patients aged 65-74 years compared to those aged ≥75 years (P=0.00). However, survival rates were largely comparable between age groups after stratification for treatment in both stages (figure 2, figure 3, and supplemental table 1). Outcomes of risk of death adjusted for gender, age, histology, and treatment are displayed in Table 2. Patients with stage IIIA

NSCLC receiving surgery showed a decreased adjusted hazard of death compared to chemoradiotherapy (HR 0.75 (95%CI 0.66-0.85) and HR 0.82 (95%CI 0.68-0.987) respectively for patients aged 65-74 years and ≥75 years). The application of radiotherapy alone showed an increased hazard of death compared to chemoradiotherapy (HR 1.9 (95%CI 1.6-2.2) and HR 1.6 (95%CI 1.4-1.9) respectively for patients aged 65-74 years and ≥75 years), and for chemotherapy alone the HRs were the same for both age groups (HR 2.2 (95%CI 1.9-2.5)). The highest adjusted risk of death was seen with BSC, which was more profound among patients aged 65-74 years (HR 4.8 (95%CI 4.1-5.5)) compared to those aged ≥75 years (HR 3.7 (95%CI 3.2-4.2)). For stage IIIB, adjusted hazards of death were higher after the application of radiotherapy alone (HR 2.5 (95%CI 1.1-3.0) for patients aged 65-74 years and HR 1.8 (95%CI1.5-2.1) for those aged ≥75 years) as compared to chemoradiotherapy. The increased hazard of death was also seen for chemotherapy alone (HR 2.3 (95%CI 2.3 (2.0-2.6) and HR 1.8 (95%CI1.5-2.2) for age groups 65-74 years and ≥75 years, respectively).

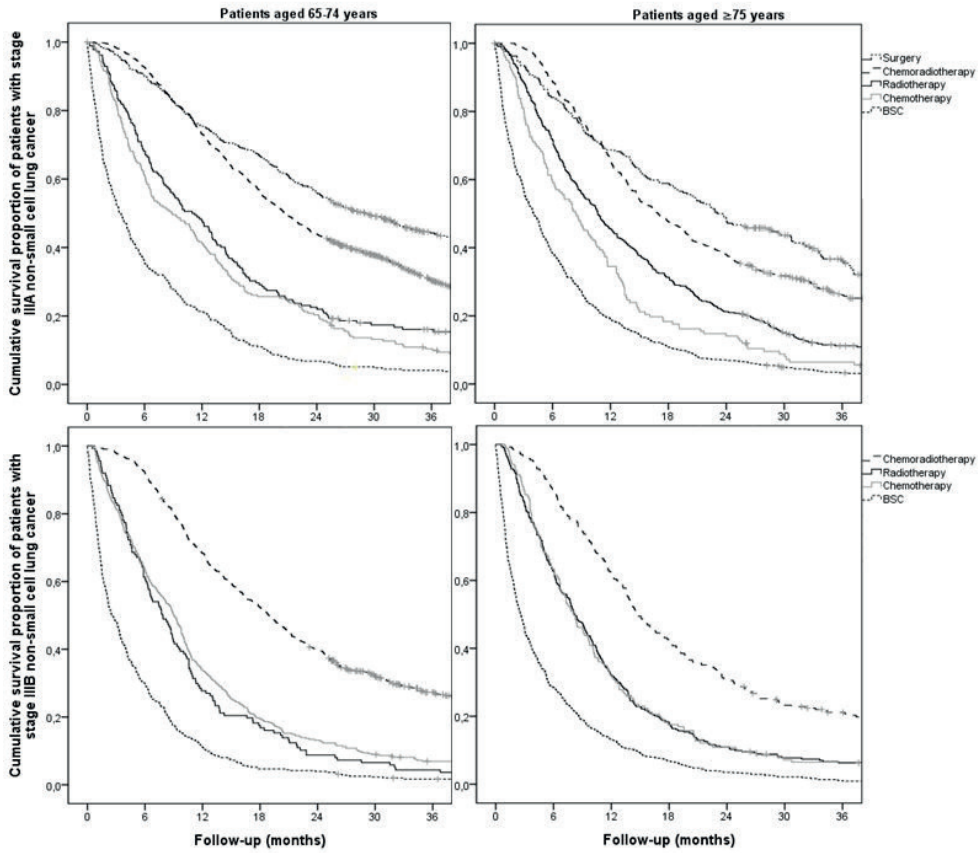


Figure 3. Kaplan-Meier survival curves of older patients diagnosed with stage III non-small cell lung cancer (2009-2013) according to obtained treatment, stage, and age groups (BSC 'best supportive care')

Number at risk	Age 65-74 years							Age ≥75 years						
after n months	0	6	12	18	24	30	36	0	6	12	18	24	30	36
Stage IIIA														
Surgery	447	402	337	299	250	219	190	214	180	147	126	103	91	71
Chemoradiotherapy	1015	941	742	576	446	384	302	427	379	283	203	162	135	107
Radiotherapy	182	124	87	53	41	31	28	422	304	193	133	89	64	44
Chemotherapy	227	140	94	59	47	31	24	141	83	48	26	20	12	9
BSC	289	100	58	28	15	9	7	595	221	102	53	33	24	15
Stage IIIB														
Chemoradiotherapy	781	718	532	407	309	248	197	265	228	161	112	81	62	55
Radiotherapy	137	84	38	24	12	9	6	293	184	94	53	32	23	18
Chemotherapy	381	242	128	74	50	34	27	169	107	54	29	18	12	11
BSC	353	97	34	14	11	7	5	607	163	73	36	18	12	6

The highest adjusted risk of death was seen for BSC (HR 6.2 (95%CI 5.4-7.1) and HR 3.9 (95%CI 3.3-4.5) for age groups 65-74 years and ≥75 years, respectively). In additional multivariable analyses including comorbidity and treatment, it was found that neither the number of comorbid conditions nor the type of comorbidity were significantly associated with survival in any age or stage group (data not shown; p=0.07 and higher). Also, changes in HRs of death for treatment types were minimal when comorbidity was included.

Table 2. Multivariable cox proportional hazard ratios of older patients diagnosed with stage III non-small cell lung cancer (2009-2013) according to stage and age groups

Stage		IIIA		IIIB	
Age yrs	**HR (95%CI)**	**65-74**	**≥75**	**65-74**	**≥75**
Treatment*	Chemoradiotherapy	*Ref*	*Ref*	*Ref*	*Ref*
	Surgery	0.75 (0.66-0.85)	0.82 (0.68-0.987)	-	-
	Radiotherapy	1.9 (1.6-2.2)	1.6 (1.4-1.9)	2.5 (2.1-3.0)	1.8 (1.5-2.1)
	Chemotherapy	2.2 (1.9-2.5)	2.2 (1.8-2.7)	2.3 (2.0-2.6)	1.8 (1.5-2.2)
	BSC	4.8 (4.1-5.5)	3.7 (3.2-4.2)	6.2 (5.4-7.1)	3.9 (3.3-4.5)
Age	yrs	1.02 (0.999-1.03)	*NA*	*NA*	*NA*
Gender	Male	*Ref*	*Ref*	*NA*	*NA*
	Female	0.87 (0.79-0.96)	0.86 (0.77-0.96)		
Histology	Squamous CC	*Ref*	*Ref*	*Ref*	*NA*
	Adenocarcinoma	0.86 (0.77-0.96)	0.87 (0.77-0.98)	0.72 (0.65-0.82)	
	NOS/large CC	0.98 (0.87-1.1)	0.95 (0.84-1.1)	0.91 (0.80-1.03)	

Abbreviations: HR 'Hazard Ratio', 95%CI '95% Confidence Interval', BSC 'Best Supportive Care', CC 'Cell Carcinoma', NOS 'Not Otherwise Specified', yrs 'years', NA 'Not Applicable' (not significant according to backward selection). *Treatment options: surgery (with and without (neo)adjuvant chemotherapy, adjuvant (stereotactic) radiotherapy, or adjuvant radiotherapy with sensitizer); chemoradiotherapy (with and without adjuvant surgery); (stereotactic) radiotherapy; chemotherapy (with and without adjuvant chemotherapy, palliative radiotherapy, monoclonal antibodies, or tyrosine kinase inhibitors); best supportive care. As surgery is unconventional in clinically staged IIIB NSCLC, the numbers and percentages are not displayed. The HR is considered significant when the 95%CI is completely above or below 1.0, with HR>1.0 indicating increased hazard of death

Discussion

The aim of this study was to assess patterns of treatment and survival among unselected Dutch patients with stage III NSCLC by describing patients aged 65-74 years and those aged ≥75 years. Almost half of patients aged 65-74 years received chemoradiotherapy, while this was only one fifth among those aged ≥75 years. Higher survival rates were seen for patients aged 65-74 years compared to those aged ≥75 years, although differences between age groups largely disappeared after stratification for treatment. In both age groups, survival after radiotherapy alone, chemotherapy alone, or BSC was poorer than after the application of chemoradiotherapy or surgery with larger differences for multivariable risk of death among patients aged 65-74 years than those aged ≥75 years.

Patients with NSCLC are widely recognized as a heterogeneous population, especially in case of older age.[17] Although older age alone should not be decisive for treatment decision-making, patient preferences are equally important as high-risk factors such as comorbidity, poor performance status, inactivity, malnutrition, or cognitive impairment.[10, 18, 19] The results of the current study confirmed that curative-intent treatment options such as chemoradiotherapy and surgery were selected in half of those aged 65-74 years and for 19% to 35% of patients aged ≥75 years. Also, patients aged ≥75 years showed poorer survival compared to those aged 65-74 years in general, although survival rates were largely comparable between age groups within treatment options. While adjustment for comorbidity was performed, residual bias due to higher natural mortality rates in older patients might be of influence, as adjusting for natural mortality could lead to even lower differences in (relative) survival between age groups. Nevertheless, these findings suggest that strict but feasible selection criteria are currently applied for intensive treatment options in clinical practice. Nevertheless, current criteria could be too strict, leading to a suboptimal number of patients aged ≥75 years receiving chemoradiotherapy or surgery. Previous studies indicated that signs of vulnerability including performance status and comorbidity lead to omission of concurrent chemoradiotherapy in two thirds of those aged ≥70 years[7] and almost all aged ≥75 years, [20, 21] which is possibly due to awareness of adverse events. However, overtreatment should also be avoided. As unplanned hospitalizations, and not completing treatment are common for chemoradiotherapy,[10] especially for older patients compared to younger patients.[20] The added survival value due to intensive treatment could be less for patients aged ≥75 years than for those aged 65-74 years, as the increased risks of death for other treatment options were less pronounced in the older age group. Severe comorbidity could significantly deteriorate treatment tolerance and survival in patients receiving concurrent chemoradiotherapy.[10, 21] This was not confirmed by the current study and could be explained by the classification of comorbidity. The Adult Comorbidity Evaluation with 27 items (ACE-27) is used more often for cancer research and includes a time window of events and severity of organ decompensation, providing more insight in effects of treatment and consequently information for future treatment decision making .[22, 23] Others implicate that collineairity and greater impact of other factors such as performance status or the likeliness of dying due to NSCLC can limit the effect of comorbidity on survival. [8, 24]

Strengths of this study were the population-based design and inclusion of (practically) all patients diagnosed with stage III NSCLC between 2009 and 2013 in the Netherlands. The added value of these results to current knowledge lies in the presentation of obtained treatment and survival rendering for unselected elderly in clinical practice. Also, access to health care is equal for all citizens in the Netherlands and all costs regarding medical treatment for NSCLC are reimbursed. As the registrars at the Netherlands Cancer Registry are trained for data collection, the quality and completeness of data is very high.

Nevertheless, some limitations should be considered. Patient information regarding performance status, smoking, social situation, and geriatric characteristics was largely unavailable, and could lead to unknown biases. Information on number and type of comorbid conditions was only available in 18% of patients. Nevertheless, all patients in the Netherlands were included, providing insights in unselected older patients. While the availability of data on treatment is unique in such a large population-based database, some treatment details were largely unavailable, such as completion of treatment, toxicity, type of chemotherapy, type of radiotherapy, treatment doses, treatment intent, and time between treatments. Unfortunately, concurrent and sequential chemoradiotherapy could not be distinguished for all patients. The rather high proportion of patients diagnosed with (clinical) stage IIIB receiving chemotherapy can be explained by retrieval of obtained treatment. As toxicity data are unavailable, it is possible that chemoradiotherapy was planned while toxicities inhibited the administration of radiotherapy or further treatment. As a result, treatment of these patients was classified as chemotherapy leading to a higher proportion of patients receiving chemotherapy instead of (intended) chemoradiotherapy in clinical practice.[10] Furthermore, a minor proportion of patients diagnosed with 'wet' stage IIIB in 2009 (TNM6, stage IIIB NSCLC with malignant pleural effusion) are more likely to be treated with chemotherapy alone. Also, effects of chemotherapy could be minimal due to the aggressiveness of disease. Despite a median follow-up of ≥5 years, most patients receiving surgery and chemoradiotherapy were censored after 24 months. Although this is an appropriate follow-up time, long-term survival in these treatment groups could potentially be higher when a longer follow-up period could be taken into account. In population-based studies, the best suitable treatment option is chosen by a multidisciplinary tumour board together with the patient and ideally based on a complex interplay of patient, tumour, and geriatric factors influencing which individually can influence treatment ouctomes as well.[24] As a result, confounding by indication should be considered when interpreting data on treatment, as merely fit patients would be considered for chemoradiotherapy according to treatment guidelines.[3] Furthermore, these data are retrospective and causal relations between patient characteristics and survival could not be examined.

Evidence regarding tools for treatment selection and optimization of survival, adverse events, and quality of life are currently lacking among older patients with stage III NSCLC in clinical practice. In this heterogeneous population including the oldest and frail subgroups, more insight could be gained through geriatric assessment, where important areas of vulnerability and potential effects of treatment are covered. While evidence is relatively scarce, it is recommended for several groups of older (lung) cancer patients,[19, 25] but not yet part of standard treatment everywhere.[26, 27] With this

information, relevant matters regarding treatment selection of intensive options can be improved including lifestyle interventions.[28] Ideally, clinical trials should be performed to assess the predicitive value of multiple factors including geriatric information and contribute to evidence of the most optimal treatment option for each patient.[29] However, evidence for treatment selection is largely unavailable for patients in clinical practice, as almost 90% of older patients with lung cancer is excluded due to strict in- or exclusion criteria leading to an unrepresentative population.[6] As trials are not always suitable for older patients due to slow accrual and inclusion of selected patients only,[6] other study types should be considered as well. National prospective population-based studies with long-term follow-up and abundant information on patient characteristics and outcomes in clinical practice could provide more insight into current practice, information gaps, and directions for future research. Also, some form of geriatric assessment and measurement of quality of life should be included.

Recently, the NVALT25-ELDAPT trial (NCT02284308) has started,[27, 30] combining an observational and randomized design. Here it is aimed to improve individual treatment choices for patients with stage III NSCLC ≥75 years by reaching the optimal balance between quality of life and survival. All included patients receive extensive geriatric assessment and are classified as 'fit' or 'frail', where fit patients are invited to be randomized to concurrent or sequential chemoradiotherapy. Frail or fit patients without additional consent receive treatment according to the physician's discretion and patient preferences, representing patients in daily clinical practice. The primary outcome of both groups is quality-adjusted survival (http://www.eldapt.org/). With these initiatives, highly needed scientific evidence addressing predictive factors in a large heterogeneous population will contribute to optimizing treatment selection and outcomes.

In conclusion, patients aged ≥75 years with stage III NSCLC were less frequently treated with chemoradiotherapy and surgery as compared to patients aged 65-74 years. Although OS rates were significantly poorer for those aged ≥75 years in general, these were largely comparable between age groups within treatment options. Therefore, treatment selection seems to be adequate for the older population with stage III NSCLC, although undertreatment of the oldest group should be warranted. Evidence regarding tools to distinguish patients fit enough for chemoradiotherapy or surgery are necessary to optimize treatment selection, survival, adverse events, and quality of life for the heterogeneous group patients with stage III NSCLC aged 65-74 years and especially ≥75 years in daily clinical practice.

Supplemental table 1 Overall survival rates and median overall survival of older patients diagnosed with stage III non-small cell lung cancer (2009-2013) according to obtained treatment, stage, and age groups

Stage	**IIIA**		**IIIB**	
Age yrs	**65-74**	**≥75**	**65-74**	**≥75**
1-year OS % (95%CI)	61 (59-63)	43 (41-45)	45 (43-48)	30 (27-32)
Treatment*				
Chemoradiotherapy	73 (70-76)	66 (62-71)	68 (65-71)	61 (55-67)
Surgery	75 (71-79)	69 (62-75)	-	-
Radiotherapy	48 (41-55)	46 (41-50)	28 (20-35)	32 (27-37)
Chemotherapy	41 (35-48)	35 (27-42)	34 (29-38)	32 (25-39)
BSC	21 (17-26)	19 (16-22)	11 (8.0-14)	13 (10-16)
3-year OS % (95%CI)	27 (25-28)	14 (13-16)	16 (14-17)	7.7 (6.2-9.1)
Treatment*				
Chemoradiotherapy	31 (28-34)	26 (22-30)	26 (23-29)	21 (16-26)
Surgery	44 (40-49)	35 (29-41)	-	-
Radiotherapy	16 (11-21)	11 (7.9-14)	4.4 (1.0-7.8)	6.1 (3.4-8.9)
Chemotherapy	11 (6.6-15)	6.3 (2.3-10)	7.1 (4.5-9.7)	6.8 (2.9-11)
BSC	3.9 (1.7-6.1)	3.3 (2.0-4.8)	1.8 (0.5-3.2)	1.1 (0.3-1.9)
Median OS months (95%CI)	16 (15-17)	9.7 (8.9 -11)	10 (9.5-11)	6.4 (5.5-7.3)
Treatment*				
Chemoradiotherapy	21 (19-22)	17 (15-19)	19 (17-20)	15 (12-17)
Surgery	29 (27-31)	23 (20-26)	-	-
Radiotherapy	11 (8.5-14)	11 (9.2-12)	7.9 (5.8-9.9)	8.2 (6.5-9.9)
Chemotherapy	9.3 (7.0-12)	8.4 (6.2-11)	9.0 (7.6-10)	8.1 (6.1-10)
BSC	3.3 (2.1-4.5)	3.9 (3.1-4.7)	2.2 (1.5-3.0)	2.4 (1.8-3.1)

Abbreviations: 95%CI '95 percent Confidence Interval', BSC 'Best Supportive Care', OS 'Overall Survival', yrs 'years'. *Treatment options: surgery (with and without (neo)adjuvant chemotherapy, adjuvant (stereotactic) radiotherapy, or adjuvant radiotherapy with sensitizer); chemoradiotherapy (with and without adjuvant surgery); (stereotactic) radiotherapy; chemotherapy (with and without adjuvant chemotherapy, palliative radiotherapy, monoclonal antibodies, or tyrosine kinase inhibitors); best supportive care. As surgery is unconventional in clinically staged IIIB NSCLC, the percentages, months, and 95%CI are not displayed

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Chapter 6

Lung cancer in the oldest old: nation-wide study in the Netherlands

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Abstract

Introduction: An important step in improving research and care for the oldest patients with lung cancer is analyzing current data regarding diagnostic work-up, treatment choices and survival.

Methods: We analyzed data on lung cancer from the Netherlands Cancer Registry (NCR –IKNL) regarding diagnostic work-up, treatment and survival in different age categories; the oldest old (≥85 years of age) versus those aged 71-84 (elderly) and those aged ≤70 years (younger patients).

Results: 47,951 patients were included in the 2010-2014 NCR database. 2,196 (5%) patients were aged ≥85years. Histological diagnosis was obtained significantly less often in the oldest old (38%, $p<0.001$), and less standard treatment regimen was given (8%, $p<0.001$) compared to elderly and younger patients. 67% of the oldest old received best supportive care only versus 38% of the elderly and 20% of the younger patients ($p<0.001$). For the oldest old receiving standard treatment, survival rates were similar in comparison with the elderly patients. In the oldest old, no survival differences were found when comparing standard or adjusted regimens for stage I and IV NSCLC; for stage III, oldest old receiving standard treatment had longer survival. No oldest old patients with stage II received standard treatment.

Conclusion: Clinicians make limited use of diagnostics and invasive treatment in the oldest old; however selected oldest old patients experienced similar survival rates as the elderly when receiving some form of anticancer therapy (standard or adjusted). More research is needed to further develop individualized treatment algorithms.

Introduction

In the Netherlands, over 12,000 patients are diagnosed with lung cancer annually.[1] Lung cancer is predominantly a disease of the elderly, as half of the patients are over 70 years of age at time of diagnosis and 30% is older than 75 years.[1] This proportion is expected to rise even further in the coming decades due to ageing of Western societies and increasing quality of medical care.[1,2]

It is a challenge to select the optimal treatment for elderly patients.[3–5] They represent a heterogeneous population due to the individual process of aging; resulting in a great variety in comorbidity, physiological reserves, geriatric syndromes and functionality.[6] In addition, due to stringent restrictions per organ system, the (especially frail) elderly are often excluded from participation in clinical trials.[7] The assumption that trial results are also valid in a population other than the studied population may not be correct.[8] Therefore, decision-making in frail or elderly patients often depends on opinions of individual team members of the multidisciplinary team.[9]representation of patients' views, and dealing with disagreements in MDT meetings-issues that affect clinical decision making, but have not previously been addressed. METHODS: Responses to open questions from a 2009 national survey of MDT members about effective MDT working in the United Kingdom were analyzed for content. Emergent themes were identified and tabulated, and verbatim quotes were extracted to validate and illustrate themes. RESULTS: Free-text responses from 1,636 MDT members were analyzed. Key themes were: (1 This could both lead to overtreatment and undertreatment of individual patients.[10]multidisciplinary cancer conferences (MCCs Specific guidelines regarding treatment of lung cancer in frail and elderly patients are scarce.[11]

An important step in improvement of clinical care in the oldest patients with lung cancer is analyzing current clinical practice and outcomes in this population. For this purpose, we analyzed patient data on lung cancer from a nationwide registry in the Netherlands, regarding diagnostic work-up, treatment choices and survival in different age categories: the oldest old (≥85 years of age), the elderly (71-84 years) and younger patients (18-70 years).

Methods

Design and patients

To analyze lung cancer care in the oldest old, we retrieved data from patients with NSCLC or SCLC aged 18 years and older from the Netherlands Cancer Registry (NCR) between 2010 and 2014. The NCR is a nationwide cancer registry that contains information on tumour characteristics and initial treatment of all newly diagnosed malignancies in the Netherlands. Data comes from a national pathology database supplemented by data from medical records, collected by trained registry personnel. Survival data are available through linkage of the Cancer Registry data with municipal population registries.[1] Follow-up was completed until February 1, 2016.

Data analysis

The NCR provided information per patient on: age, sex, histological diagnosis (non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) or no histological diagnosis), clinical tumour staging according to Tumour Node Metastasis classification (cTNM)[12,13], acquired initial treatment (surgery, (stereotactic body)radiotherapy, chemoradiotherapy, chemotherapy, targeted therapy or best supportive care), follow-up (in days) and vital status (alive or not). In this audit, we compared treatment as recorded at the NCR with guideline recommended treatment. An overview of Dutch guidelines for treatment of lung cancer can be found in the Appendix.[12,13] In summary: surgical resection is advised for stage Ia and Ib non-small cell lung cancer (NSCLC). Adjuvant chemotherapy is not recommended for stage Ia, but is advised to consider for stage Ib. For stage II surgical resection with adjuvant chemotherapy is advised. Concurrent chemoradiotherapy, or sequential chemoradiotherapy depending on the size and location of the tumour, is advised for stage III NSCLC, as well as for limited disease small cell lung cancer (SCLC). For selected patients with stage III surgical resection in combination with (neo)-adjuvant chemo- or radiotherapy is stated to be considered as standard treatment. Chemotherapy alone is recommended for all patients with stage IV NSCLC and for extended disease SCLC. For patients with NSCLC and an ECOG PS of 3 or 4 best supportive care only is recommended, for SCLC guideline recommend best supportive care only in case of an ECOG PS of 4. In the present guidelines, age and frailty are not considered to be determinants for choice or adjustment of therapy.[12,13]

Diagnostic work-up was classified as according to guidelines if the disease stage was known and if a histological diagnosis was available. We classified therapy as 'standard treatment' when in line with guideline recommended treatment. Treatment was classified as 'adjusted treatment' when patients received some form of oncologic therapy, but adapted from the guideline recommendation. Treatment was classified as 'best supportive care only' (BSC) when patients received best supportive care only or no treatment at all. Patients were excluded from further analyses when it was impossible to categorize treatment due to lack of information. Unfortunately, no information about ECOG PS was available.

Statistical analysis

To assess outcomes regarding diagnostic work-up, treatment choices and survival of lung cancer care in the oldest old (85 years and older), a comparison is made between these patients, those aged between 71 and 84 years ('elderly') and those aged between 18 and 70 years ('younger'). Overall survival analyses are described as proportion of patients alive after one, two and three years. When groups consisted of less than 10 patients, no further survival analyses were performed. All analyses were performed in SPSS Statistics version 23.0. For comparisons between groups, the chi-square test is used for nominal and ordinal variables, and the ANOVA test is used for continuous variables. Normally distributed data are presented as mean with standard deviation and non-normally distributed numbers are presented as median with interquartile range (IQR). A p-value smaller than 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 47,951 patients with lung cancer were included in the 2010-2014 NCR database (Table 1). The oldest old (≥85 years) consisted of 2,196 (5%) patients, 18,686 (39%) were aged between 71-84 years and 27,069 (57%) were younger than 70 years of age. The median age of included patients was 69 years (interquartile range: 61-76 years) and 60% was male.

Diagnosis

Figure 1 shows differences in diagnostic work-up for lung cancer among the oldest old (≥85), elderly (71-84) and younger patients (≤70). For the oldest old, no histological diagnosis was obtained in 38% of patients, versus 14% in the elderly and 5% in the younger group (p<0.001). Of the 2,196 oldest old, 1,197 (55%) patients were diagnosed with NSCLC and 168 (8%) with SCLC. Tumour staging was also significantly more often incomplete in the oldest old (Figure1): the NSCLC disease stage was unknown in 3.3% of the patients aged 85+ versus 1.3% of the elderly and 0.4% of the younger patients (p<0.001) For patients with SCLC, numbers of oldest old patients were too small for analyses.

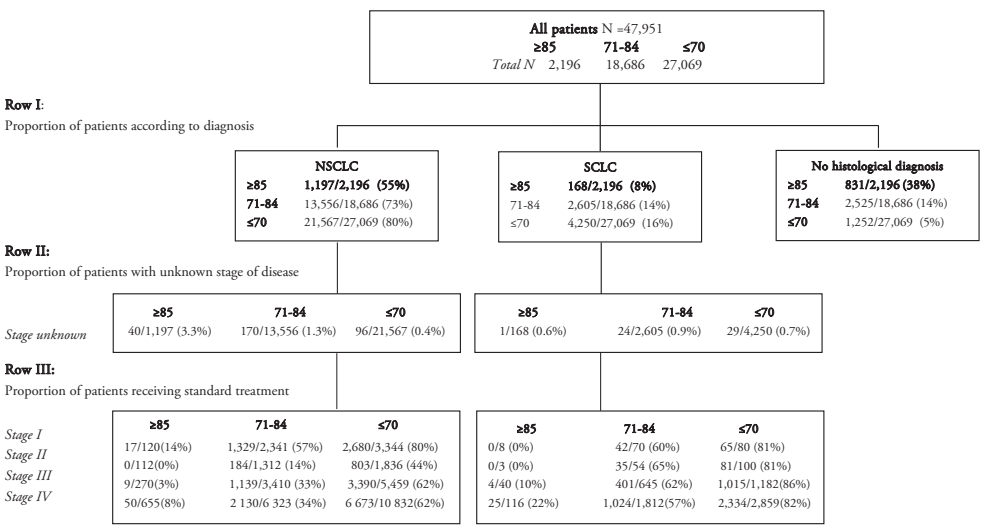

Figure 1. Flowchart diagnostic work-up and treatment choice. Percentages in Row I represent the proportion of patients within each age group with that particular diagnosis. In Row II, percentages represent the proportion of patients with particular diagnosis per age group with unknown stage of disease. Percentages in Row III represent the proportion of patients within each age group that received standard treatment as recommended for that particular diagnosis and disease stage. Numbers are displayed as number/total number (percentage). Abbreviations: '(N)SCLC' (non) small cell lung cancer, 'N' number

Table 1. Baseline characteristics of patients with lung cancer according to age category

		≤70 years		71-84 years		≥85 years		p-value
	Number of patients	**27,069**		**18,686**		**2,196**		
Sex	Male, n (%)	14,716	(54%)	12,569	(67%)	1,461	(67%)	<0.001
Age	Median (IQR)	62	(57-66)	76	(73-80)	87	(86-88)	
Diagnosis, n (%)	NSCLC	21,567	(80%)	13,556	(73%)	1,197	(55%)	<0.001
	SCLC	4,250	(16%)	2,605	(14%)	168	(8%)	
	No histological diagnosis	1,252	(5%)	2,525	(14%)	831	(38%)	
Disease stage, n (%)	I	3660	(14%)	2782	(15%)	205	(9%)	<0.001
	II	1975	(7%)	1451	(8%)	149	(7%)	
	III	6,719	(25%)	4,251	(23%)	404	(18%)	
	IV	13,927	(51%)	8,614	(46%)	957	(44%)	
	Unknown	788	(3%)	1,588	(9%)	481	(22%)	
Treatment for NSCLC and SCLC*, n (%)	Standard treatment	17,041	(66%)	6,283	(39%)	105	(8%)	<0.001
	Adjusted treatment	3,617	(14%)	3,710	(23%)	348	(25%)	<0.001
	Best supportive care only	5,141	(20%)	6,155	(38%)	912	(67%)	<0.001

*Patients with no histological diagnosis were excluded from analyses. IQR: interquartile ranges, (N)SCLC: (non) small cell lung cancer

Standard treatment according to guidelines

Patients without a histological diagnosis (4,608 out of 47,951 patients, 9.6%) were excluded from analyses regarding treatment guideline adherence. Of these patients, 68% received best supportive care only.In those with a histological diagnosis (NSCLC or SCLC), standard treatment was given significantly more often to the elderly and younger patients than to the oldest old (Fig. 1 and Table 1): only 8% received standard treatment compared to 39% of the elderly and 66% of the younger patients (p<0.001). In addition, regardless of tumour type or disease stage, 67% of the oldest old received best supportive care only versus 38% of the elderly, and 20% of the younger patients (p<0.001). The remaining patients received an adjusted treatment regimen: 25% of the oldest old, 23% of the elderly and 14% of the younger patients.

Overall survival

Survival analyses were performed separately for each histological subgroup (NSCLC, SCLC, no histological diagnosis). For patients without a histological diagnosis, survival after one year was 23% in the oldest old, 35% in the elderly and 45% in the younger patients (p<0.001).

One and two year survival analyses of the oldest old with NSCLC according to treatment strategy and tumour stage are visualized in Figure 2a and 2b, respectively. One year survival in the oldest old with stage I NSCLC receiving standard treatment was 76% (13/17) compared to 95% (2,509/2,655) in younger patients with stage I NSCLC

(p=0.02), while no significant difference could be observed comparing the oldest old with the elderly (89%, 1,175/1,321; p=0.2). No analyses could be performed for stage II and III due to limited numbers of patients receiving standard treatment. For stage IV NSCLC, no significant differences in survival among the different age categories for patients receiving standard treatment were observed either: for the oldest old, one year survival with standard treatment was 46% (23 out of 50), compared to 36% (770 out of 2,131) for the elderly and 36% (2,372 out of 6,680) for the younger patients (p=0.35).

As visualized in Figure 2a and b, one and two year survival did not differ significantly for stage I NSCLC between the oldest old receiving standard treatment and oldest old receiving adjusted treatment – i.e. radiotherapy instead of surgical resection (both 77% and 57-65%, respectively). For the oldest old with stage I, after three years 47% of patients (8 out of 17) were alive compared to 42% of patients who received adjusted treatment (32 out of 76).

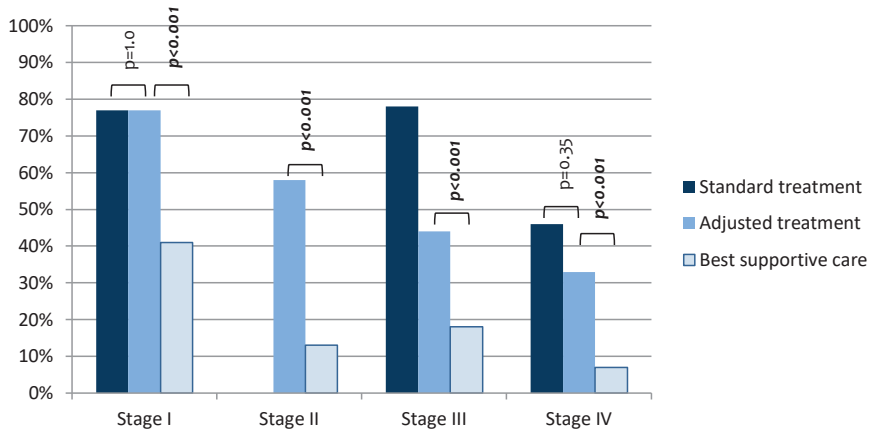

Figure 2a. One year survival of the oldest old (85+) with non-small cell lung cancer

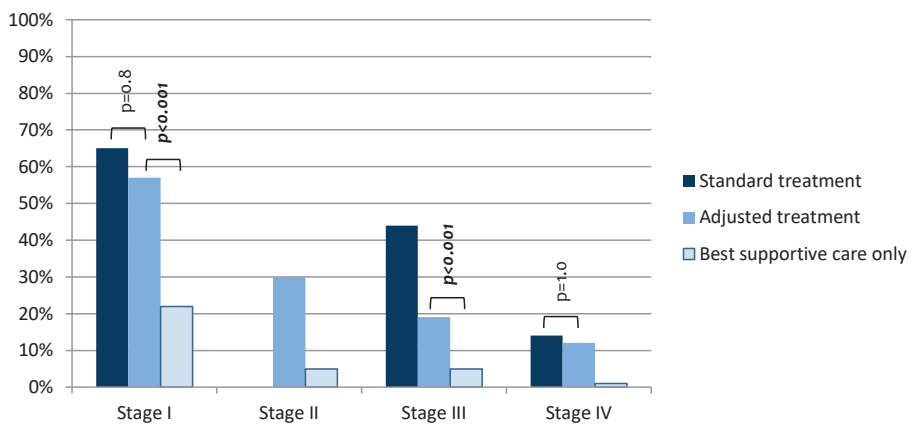

Figure 2b. Two year survival of the oldest old (85+) with non-small cell lung cancer

For stage IV, no significant differences were observed between patients receiving standard treatment versus adjusted treatment – i.e. radiotherapy or surgical resection instead of palliative chemotherapy (two year survival 14% and 12%, respectively; p=1.0). No significant differences could be found after three years either (4% and 2%, p=0.6). Due to limited numbers of patients receiving standard treatment these analyses could not be performed for stage II and III.

For all disease stages, best supportive care only resulted in a significantly poorer survival (Figure 2A), with similar survival rates compared to other age groups (data not shown).

For the SCLC population, numbers of patients were too small for meaningful subgroup analyses per disease stage, one year survival was 9% (15 out of 168) in the oldest old, 21% (545 out of 2,605) in the elderly and 40% (1,703 out of 4,249) for younger patients (p<0.001).

Discussion

In this study, using the 2010-2014 Netherlands Cancer Registry (NCR) database, a total of 2,196 patients of 85 years and older were identified, which makes this study one of the first describing clinical practice in such a large cohort of oldest old patients with lung cancer. It was found that in this population, physicians generally limited diagnostic work-up and use of invasive treatment. More often no histological diagnosis was obtained and, regardless of disease stage, the majority received best supportive care only (67%) or an adjusted treatment regimen (25%). However, for the selected minority of oldest old who did receive standard treatment, survival rates were similar in comparison with elderly patients. Of note, no differences were observed in one and two year survival between the oldest old with NSCLC who received standard treatment in comparison to an adjusted regimen (stage I and IV); however, survival was significantly worse in those receiving best supportive care only.

Due to the large nation-wide coverage of the NCR, over 95% of the patients diagnosed with lung cancer within the 2010 and 2014 timeframe from the Netherlands are included in this database. Our results regarding diagnostic work-up and treatment are largely in line with previous research, focusing on clinical practice in the older lung cancer patients.[14–16]evidence is scarce regarding motives and effects of treatment modalities. METHODS: Hospital-based multicenter retrospective study including unresectable stage III NSCLC patients aged 70 and diagnosed between 2009 and 2013 (N=216 Comparing treatment choices in older patients showed international differences. A Canadian study, in which 29,515 patients with lung cancer younger than 70 years were compared with 32,131 patients older than 70 years, concluded that microscopic information of the disease lacked more frequently in the elderly and referral to an oncologist occurred significantly less often.[17] Studies performed in Sweden and Japan among octogenarians (patients aged 80 years and older) with lung cancer found that 46% received no treatment or best supportive care only[18–20]an increasing proportion of cancer patients are aged >65 years and many are aged >70 years. Treatment of the elderly with lung cancer has, therefore, become an important issue. We performed a

retrospective study of our patients to demonstrate how octogenarians with non-small cell lung cancer (NSCLC. This proportion was lower in a retrospective American study among 111 octogenarians with stage I-IV lung cancer, where only 11% received best supportive care.[21]patients aged 80 or older have inferior survival. Treatment practices in this patient population are poorly described. In this report, we describe the treatment of a population of very elderly patients with NSCLC at a large teaching hospital. METHODS: A retrospective chart review was performed of 111 outpatients with NSCLC aged 80 or older. Patient treatment regimens were evaluated for consistency with contemporaneous stage-specific guideline-recommended therapy (GRT A possible explanation for the higher proportion of administered best supportive care only (74%) among the oldest old, could be the age limit of 85 years instead of 80 used in the other studies. In addition, cultural aspects regarding medical care late in life could also be an important factor for this inequality.[22,23]

Analyzing current clinical practice can aid in identifying aspects of lung cancer care and research that are amenable for improvement. We found that in the minority of the oldest old patients who receive some form of anticancer therapy (be it standard treatment or an adjusted regimen), survival rates were comparable to those in patients aged 71-84 years demonstrating that selected oldest old are able to benefit from oncologic therapy. This subsequently leads to the important question of how to identify these individuals within the heterogeneous oldest old population, with its extensive variety in comorbidities, physiological reserves and frailty.[24,25] Treatment guidelines and currently available research give little support as to the criteria on which this selection should ideally be based.

Unfortunately, the NCR database does not contain data regarding patient specific factors such as comorbidity, functional reserves, presence of geriatric syndromes or ECOG PS. These factors are key-issues in the decision-making process regarding diagnosis and treatment as well as for outcome.[6,25,26,14,15,27,28]" Due to lack of this information, it was not possible to identify which patient characteristics are associated with receiving standard treatment or having longer survival. In addition, no information was available about toxicity, treatment completion or the patients' perspective regarding satisfaction with treatment. As a result of these limitations, we are unable to translate our findings into individual treatment algorithms or stratification models. Another limitation of this study is that when comparing treatment regimens (standard vs. adjusted), we are comparing selected patient populations, particularly in the oldest old, where a significant proportion had no histological diagnosis or inadequate staging. While this is a reflection of actual clinical practice, and the data are real life data, it is important to keep this selection in mind when interpreting these results.

Despite these limitations, data do suggest two important areas of future research. First of all, research should focus on identifying those patient-related factors that differentiate between those who are able to benefit from treatment from those for whom best supportive care is the best option. For this purpose, the International Society of Geriatric Oncology has suggested the use of a geriatric assessment, [26] which is a systematic procedure for detecting previously undiagnosed medical conditions and

geriatric syndromes, such as care dependence, mobility issues, cognitive impairments or malnutrition.[5,26] Prior research in lung cancer demonstrated that using geriatric assessment for selecting treatment intensity resulted in less aggressive treatment and less toxicity without affecting survival.[29]

Another area for improvement would be the incorporation of patient reported outcome measures (PROMs) in clinical research.[30,31] Especially for the oldest old, PROMS such as maintaining independence, cognitive function and quality of life are highly relevant when trying to balance risks and benefits.[32,33] Multiple previous studies have demonstrated that older patients with cancer are generally less willing to accept toxicity for additional survival time, especially when therapy negatively influences their quality of life or functional status.[14,15,30,31,34] At the moment PROMs are incorporated only in a minority of clinical trials,[33]for currently recruiting phase I, II, or III clinical trials in lung cancer. Trial characteristics and study objectives were extracted from the registry website. RESULTS: Of the 419 clinical trials included in this review, patient-centered outcome measures are investigated in a minority of the trials. Outcome measures as quality of life, functional capacity, and health care utilization are included in a small number of trials (20, 4, and 2 % respectively despite the fact that, nearly two decades ago, the Federal Drug Administration (FDA) and European Organization for Research and Treatment of Cancer (EORTC) guidelines have made inclusion of quality of life mandatory in all new clinical trial proposals in diseases with a poor prognosis.[35–37] Improving lung cancer care needs to be accomplished by multidimensional changing; incorporation of these suggested interventions can lead to great progress in current clinical practice and will be helpful for advising patients prior to start of treatment.

In conclusion, lung cancer is primarily a disease of older patients, although only a minority is older than 85 years; this is one of the first studies describing a cohort of over 2,000 oldest old with lung cancer. Clinicians make limited use of diagnostics and invasive treatment in this patient population. However, selected patients experienced similar survival rates to the elderly when receiving some form of anticancer therapy (standard or adjusted). More research is needed to be able to identify key-issues for the development of individualized treatment algorithms to help improving the complex decision making process for patients with lung cancer.

Appendix

Summary of Dutch lung cancer guideline recommended treatment

	Summary of Dutch guidelines for standard treatment of pulmonary malignancies according to tumour stage	
NSCLC		
	Stage Ia	Surgical resection
	Stage Ib	Surgical resection *
	Stage II	Surgical resection with adjuvant chemotherapy
	Unforeseen pN2 or pN3	Surgical resection with adjuvant radiotherapy
	Tumour cells in resection	Adjuvant radiotherapy
	Stage III	Concurrent chemoradiation therapy, for selected patients surgical reseection with adjuvant therapy is stated to be considered
	Stage IV	Palliative chemotherapy**
SCLC		
	Limited disease	Chemoradiation therapy
	Extensive disease	Palliative chemotherapy
	In case of response to chemotherapy	Prophylactic cranial irradiation
NSCLC	WHO PS 3 or 4	Best supportive care
SCLC	WHO PS 4	Best supportive care

(N)SCLC: (non) small cell lung cancer

WHO PS: World Health Organization Performance Score

* Guideline is ambivalent according treatment with adjuvant chemotherapy in stage IB

** Targeted therapy with tyrosine kinase inhibitor if mutation in EGFR or ALK is found

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Part 2

Patient characteristics for treatment tolerance and survival

Chapter 7

Stage III non-small cell lung cancer in the elderly: Patient characteristics predictive for tolerance and survival of chemoradiation in daily clinical practice

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Abstract

Background: In unselected elderly with stage III Non-Small Cell Lung Cancer (NSCLC), evidence is scarce regarding motives and effects of treatment modalities.

Methods: Hospital-based multicenter retrospective study including unresectable stage III NSCLC patients aged ≥70 and diagnosed between 2009-2013 (N=216). Treatment motives and tolerance (no unplanned hospitalizations and completion of treatment), and survival were derived from medical records and the Netherlands Cancer Registry.

Results: Patients received concurrent chemoradiation (cCHRT, 33%), sequential chemoradiation (sCHRT, 24%), radical radiotherapy (RT, 16%) or no curative treatment (27%). Comorbidity, performance status (58%) and patient refusal (15%) were the most common motives for omitting cCHRT. Treatment tolerance for cCHRT and sCHRT was worse in case of severe comorbidity (OR 6.2 (95%CI 1.6-24) and OR 6.4 (95%CI 1.8-22), respectively). One-year survival was 57%, 50%, 49% and 26% for cCHRT, sCHRT, RT and no curative treatment, respectively. Compared to cCHRT, survival was worse for no curative treatment (P=0.000), but not significantly worse for sCHRT and RT (P=0.38).

Conclusion: Although relatively fit elderly were assigned to cCHRT, treatment tolerance was worse, especially for those with severe comorbidity. Survival seemed not significantly better as compared to sCHRT or RT. Prospective studies in this vital and understudied area are needed.

Introduction

Thirty percent of all Non-Small Cell Lung Cancer (NSCLC) patients present with stage III disease [1, 2]. A meta-analysis including clinical trials showed the superiority of concurrent chemoradiation (cCHRT) to sequential chemoradiation (sCHRT) for unresectable stage III NSCLC, with a 2- and 5-year survival of 36% and 15% for cCHRT and 30% and 11% for sCHRT [2]. Mainly fit patients with minimal or no comorbidity were included and only 16% was aged ≥70. Nevertheless, cCHRT is considered standard treatment [2-5]. Alternative curative treatment options are sCHRT [6-8] and radical radiotherapy (RT) [9, 10]. Symptom relief and preservation of Quality of Life (QoL) is offered to patients not eligible for curative options by palliative care or best supportive care [7, 11].

NSCLC is diagnosed at a median age of 70 years and the majority of these patients are poor-risk, indicating poor characteristics for treatment tolerance and prognosis [12, 13]. Risk factors for poor treatment tolerance include poor general Performance Status (PS), polypharmacy, frailty, history of smoking, and extensive smoking-related comorbidity. Other geriatric characteristics such as living situation and functional disability can jeopardize treatment outcomes even more [14-18]. As a result, severe adverse events may occur more often, leading to reduced treatment dose, treatment discontinuation, hospitalization or even death [2, 7, 13, 19]. In clinical trials, evidence for treatment regimens is generally assessed in relatively fit and younger patients. These data cannot be extrapolated to the heterogeneous group of NSCLC patients in clinical practice, resulting in a lack of knowledge on treatment administration for elderly and poor-risk patients [12-14, 16, 20]. In some studies, subset analyses among older patients have been performed to provide information on treatment effects [1, 2, 21]. However, small sample sizes (N<50) lead to a lack of solid conclusions and the role of comorbidity, PS and other patient characteristics on treatment tolerance and survival in elderly receiving chemoradiation (CHRT) remains uncertain [7, 12, 16, 22, 23].

The aims of this study were to evaluate treatment strategies, identify motives for omitting cCHRT and determine predictors for treatment tolerance and survival in unselected elderly with unresectable stage III NSCLC in daily clinical practice.

Patients and methods

Patients were retrieved from the population-based Netherlands Cancer Registry, where trained registrars collect data from patient records like histology and stage of disease with a completeness rate of 95% [24]. All patients from three Dutch teaching hospitals were selected. Additional information on treatment motives, patient characteristics, treatment tolerance and survival was retrospectively collected from the medical records. Inclusion criteria were age ≥70 and a diagnosis of unresectable stage III NSCLC between 2009 and 2013. This period was chosen because of the new TNM staging guidelines in 2009 (TNM Lung Cancer Staging 7th edition [25]) and the ability to collect complete and good quality data retrospectively from medical records. Patients were included from January 1st 2009 until December 31st 2013 and follow-up (FU) was completed until January 31st 2015. Data handling of the unidentifiable data from the Netherlands Cancer

Registry was done according to the specifications of the officially recognized Code of Conduct Use of data in health research [26]. Due to the retrospective design, study approval by the medical ethics committee was not mandatory according to the Dutch law 'Medical Research (human subjects) Act' [27]. The following patient characteristics were categorized: Age in years (70-74, 75-79 and 80+), Body Mass Index (BMI) in kg/m² (<22, 22-28 and >28) [28], histology (adenocarcinoma, squamous cell carcinoma or large cell/Not Otherwise Specified (NOS)), comorbidity according to the Adult Comorbidity Evaluation 27 (ACE-27) (severe comorbidity (severe decompensation in one organ or moderate decompensation in ≥2 organs) and no severe comorbidity (no decompensation, mild decompensation in one organ, moderate decompensation in one organ or mild decompensation in ≥2 organs)), number of comorbid conditions (0, 1 or ≥2) and type of comorbidity (cardiovascular, respiratory or renal) [29], World Health Organization Performance Status (WHO PS) (0-1 and ≥2) and smoking (current, former and never). Social factors were coded as living independently (yes/no) and living alone (yes/no). Motives for omitting cCHRT were categorized as comorbidity and/or PS, refusal by patient, short life expectancy, high age and other.

Planned treatment options were classified as cCHRT, sCHRT, RT or no curative treatment (including palliative chemotherapy (CT), palliative RT and no active treatment). Regimens for CT consisted of two or three concurrent cis- or carboplatin based doublet cycles or three to four sequential cis- or carboplatin based doublet cycles. Platinum partner CT and number of cycles depended on local hospital protocol. For RT, Gross Tumour Volume (GTV) included the primary tumour and pathologic lymph nodes as identified on the FDG-PET scan. During the period 2009-2011, Intensity Modulated Radiotherapy (IMRT) was used, and from 2012 radiotherapy was delivered with an arc technique. Volume constraints for the esophagus were not performed, the maximum point dose in the esophagus was 76 Gy (biologically equivalent dose in 2 Gy fractions (EQD2)). The Clinical Target Volume (CTV) covered an extra margin to include regions at risk of microscopic extension. Planning Target volume (PTV) encompassed a margin for inter- and intrafraction patient and organ motion. Radical RT was defined as delivery of a minimum total tumour dose (TTD) of 54 Gy (EQD2). Possible RT schedules included 33*2 Gy (once daily), 24*2.75 Gy (once daily) or RT according to an individualized prescribed maximal tolerated dose protocol (once or twice daily). RT was delivered using 6-10 MV photons. The dose was specified at 100% in the ICRU reference point. The dose gradient was 95%-115%. Completion of CHRT was determined by receiving a minimal radiation dose of 54 Gy combined with all planned CT cycles. Completion of RT was achieved when receiving a radiation dose of at least 54 Gy. Treatment tolerance (yes/no) was classified as completion of treatment combined with no unplanned hospitalizations, including hospitalizations for acute radiation esophagitis. Since unplanned hospitalizations are more expected and accepted during cCHRT [2, 6], separate analyses were performed for 'completion of treatment' as a measure for treatment tolerance. Overall Survival (OS) was calculated from date of diagnosis of stage III NSCLC until death or until last date of FU and censored. The Consolidated Standards of Reporting Trials (CONSORT) flow-diagram is displayed in *Supplemental figure 1.*

Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics 22. Patient characteristics were described according to treatment regimen (cCHRT, sCHRT, RT or no curative treatment) and significant differences between treatment regimens were assessed by X^2-test, Fisher's exact test, or ANOVA (P<0.05 two sided). Motives for omitting cCHRT were described (N and %). Univariate and multivariate binary logistic regression analyses were performed for treatment tolerance and patient characteristics. The Odds Ratio (OR) and corresponding 95% Confidence Intervals (95%CI) were displayed. Worse tolerance was indicated by OR>1.0. For regression analysis, the backward stepwise method was used with an entry probability of 0.05 and removal of 0.10. It was assumed that treatment choice partially depended on patient characteristics ('confounding by indication'). Therefore, analyses for treatment tolerance and survival were stratified according to treatment regimen. Kaplan-Meier analyses were performed to assess median OS and significant differences between groups were assessed by the log rank test (P<0.05). Median follow-up was estimated with the reverse Kaplan-Meier method [30]. The Hazard Ratio (HR) and 95%CI were calculated by Cox regression analyses for survival and patient characteristics. Worse survival was indicated by HR>1.0. In all multivariate analyses, outcomes were determined significant if the 95%CI was completely above or below 1.0.

Table 1. Overview of patient characteristics according to administered treatment

N(%)	cCHRT 72 (33)	sCHRT 52 (24)	RT 34 (16)	NCT 58 (27)	P-value
Gender					0.58
Male	55 (76)	44 (85)	26 (77)	43 (74)	
Female	17 (24)	8 (15)	8 (24)	15 (26)	
Age (years)					0.000
70-74	39 (54)	15 (29)	3 (9)	18 (31)	
75-79	23 (32)	22 (42)	14 (41)	21 (36)	
80+	10 (14)	15 (29)	17 (50)	19 (33)	
WHO PS					0.000
0-1	69 (96)	36 (69)	20 (59)	17 (29)	
2-3	2 (3)	15 (29)	14 (41)	38 (66)	
Unknown	1 (1)	1 (2)	0 (0)	3 (5)	
Comorbidity					0.003
No severe	41 (57)	20 (39)	12 (35)	15 (26)	
Severe	31 (43)	30 (62)	22 (65)	43 (74)	
Comorbidity N					0.051
0	13 (18)	9 (17)	2 (6)	5 (9)	
1	22 (30)	8 (15)	10 (29)	9 (16)	
≥2	37 (51)	35 (67)	22 (65)	44 (76)	
Type**					
Cardiovascular	43 (60)	36 (69)	24 (71)	43 (74)	0.84
Respiratory	16 (22)	20 (38)	10 (29)	23 (40)	0.23
Renal	4 (6)	2 (4)	1 (3)	4 (7)	0.66
BMI (Kg/m²)					0.83
<22	10 (14)	5 (10)	4 (12)	8 (14)	
22-28	42 (58)	33 (64)	15 (44)	29 (50)	
>28	20 (28)	14 (27)	11 (32)	11 (19)	
Unknown	0 (0)	0 (0)	4 (12)	10 (17)	
Smoking					0.73
Current	29 (40)	18 (35)	9 (27)	22 (38)	
Former	39 (54)	33 (64)	16 (47)	26 (45)	
Never	2 (3)	1 (2)	2 (6)	3 (5)	
Unknown	2 (3)	0 (0)	7 (21)	7 (12)	
Histology					0.20
Squamous CC	23 (32)	15 (30)	5 (15)	15 (26)	
Adenocarcinoma	17 (24)	7 (14)	7 (21)	17 (29)	
NOS/ large cell	32 (44)	28 (56)	22 (65)	26 (45)	
Living independent					0.19
Independent	68 (96)	49 (94)	27 (79)	44 (76)	
Dependent	3 (4)	3 (6)	4 (12)	7 (12)	
Unknown	1 (1)	0 (0)	3 (9)	7 (12)	
Living alone					0.36
Alone	31 (43)	18 (35)	13 (38)	27 (47)	
Not alone	40 (56)	34 (65)	16 (47)	25 (43)	
Unknown	1 (1)	0 (0)	5 (15)	6 (10)	
Platinum type					0.10
Carboplatin	29 (40)	25 (48)	NA	NA	
Cisplatin	42 (58)	19 (37)			
Unknown	1 (1)	8 (15)			

Figures are displayed as N (%) 'Number (percentage)', the P-value is based on known data, abbreviations: CC 'Cell Carcinoma', cCHRT 'concurrent chemoradiation', DM 'Diabetes Mellitus', NA 'Not Applicable', sCHRT 'sequential chemoradiation', RT 'radical radiotherapy', NCT 'No Curative Treatment', WHO 'World Health Organization', NOS 'Not Otherwise Specified', ** comorbidity type : mild, moderate and severe comorbidities combined, the percentage could exceed 100% since >60% of patients have ≥2 comorbidities.

Results

A total of 216 elderly patients with unresectable stage III NSCLC were included. Seventy-two received cCHRT (33%), 52 received sCHRT (24%), 34 received RT (16%) and 58 received no curative treatment (27%). In *Table 1*, patient characteristics according to administered treatment are shown. Age≥75, PS≥2 and severe comorbidity were significantly more present in patients not receiving cCHRT (P<0.05). The most common motives for omitting cCHRT were the presence of comorbidity, a poor PS or a combination of both (57%), and refusal by the patient (15%). Other motives were short life expectancy (11%), high age (4%) and other/unknown (12%).

Most patients completed administered treatment (71%, 63% and 80% for cCHRT, sCHRT and RT, respectively (P=0.26)). Surprisingly, only 26% of patients receiving cCHRT tolerated treatment (defined as completed treatment without unplanned hospitalizations) compared to 40% for sCHRT and 59% for RT (P=0.000). Additionally, patients undergoing CHRT with severe comorbidity had significantly worse treatment tolerance compared to patients without severe comorbidity (OR 6.2 (95%CI 1.6-24) for cCHRT and OR 6.4 (95%CI 1.8-22) for sCHRT, *Figure 1* and *Table 2*). The same trend was seen in patients with ≥2 comorbid conditions compared to no comorbidity (OR 7.1 (95%CI 1.6-32) for cCHRT and OR 6.5 (95%CI 1.3-32) for sCHRT). No other significant associations between treatment tolerance and characteristics were found.

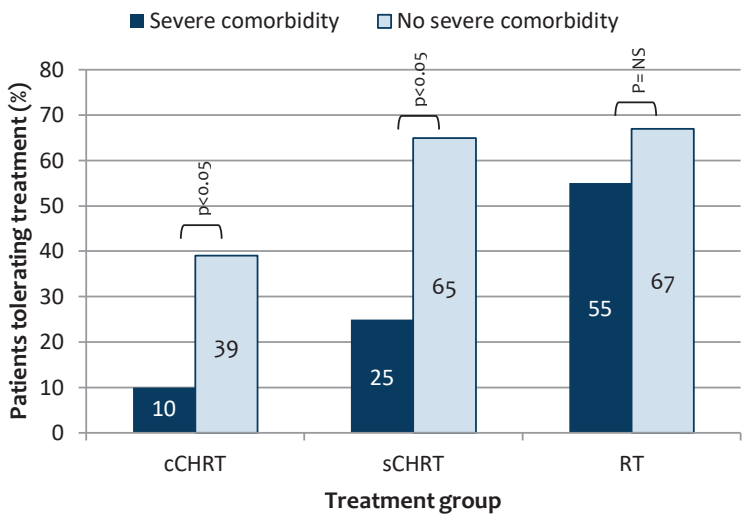


Figure 1 .Percentage of patients tolerating treatment (completion of treatment and no unplanned hospitalizations) per treatment and comorbidity group. Abbreviations: cCHRT 'concurrent chemoradiation', sCHRT 'sequential chemoradiation', RT 'radical radiotherapy', NS ' Not Significant'

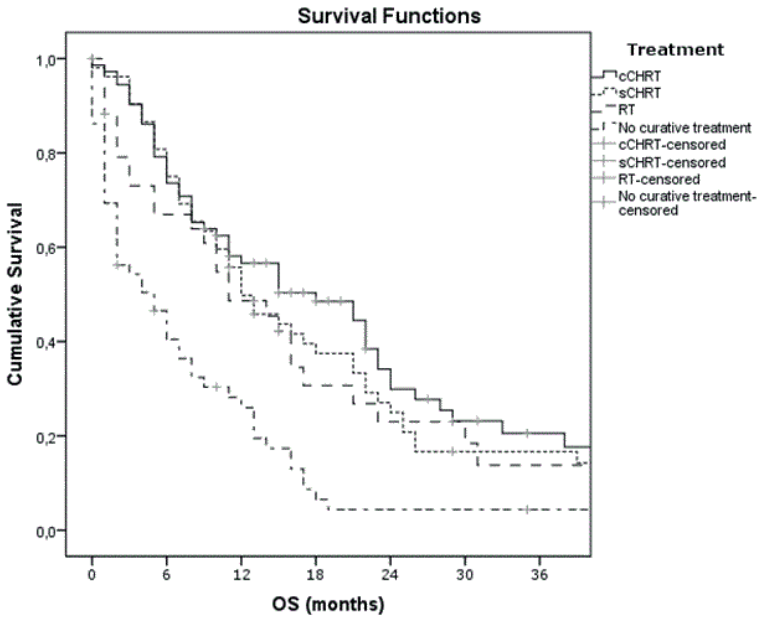
Overall median FU was 47 months. Median OS and 1- and 2-year survival for cCHRT were 18 months (95%CI 9.2-27), 57% and 21%, respectively (*Figure 2*). For sCHRT, this was 12 months (95%CI 7.5-17), 50% and 17%, respectively. For RT, these figures were 11 months (95%CI 5.5-16), 49% and 14%, respectively, and for no curative treatment 5 months (95%CI 1.6-8.4), 26% and 4%, respectively.

Table 2. Odds Ratios (ORs) for predictors of treatment tolerance stratified for cCHRT and sCHRT (treatment tolerance = completion of treatment and no unplanned hospitalizations)

Predictor	Unadjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
cCHRT				
Age				
70-74	*Reference*			
75-79	0.69 (0.22-2.2)	0.52	*NA*	
80+	0.70 (0.15-3.3)	0.65		
WHO PS				
0-1	*Reference*			
2-3	*NA*	0.99	*NA*	
Comorbidity				
No severe	*Reference*		*Reference*	
Severe	6.0 (1.6-23)	0.009	6.2 (1.6-24)	0.008
sCHRT				
Age				
70-74	*Reference*			
75-79	1.1 (0.26-4.3)	0.92	*NA*	
80+	0.33 (0.08-1.5)	0.15		
WHO PS				
0-1	*Reference*			
2-3	2.2 (0.59-8.2)	0.24	NA	
Comorbidity				
No severe	*Reference*		*Reference*	
Severe	5.6 (1.6-23)	0.006	6.4 (1.8-22)	0.004

Figures are displayed as OR (95%CI) 'Odds Ratio (95% Confidence interval)', abbreviations: cCHRT 'concurrent chemoradiation', sCHRT 'sequential chemoradiation', WHO PS 'World Health Organisation Performance Status', NA 'Not Applicable', OR>1.0 indicates worse treatment tolerance, none of the unadjusted predictors was significant for radical radiotherapy.

In multivariate analyses, OS for patients who received no curative treatment was significantly worse compared to those who received curative treatment options (HR 2.9 (95%CI 1.9-4.3) *P*=0.000). However, cCHRT did not show significant superior OS compared to sCHRT or RT (HR 1.2 (95%CI 0.82-1.8) and HR 1.3 (95%CI 0.81-2.0), respectively *P*=0.38). The stratified results of unadjusted and adjusted HRs for survival are shown in *Table 3*. Among patients receiving cCHRT, those with severe comorbidity had significant worse (median) survival compared to patients without severe comorbidity (22 months (95%CI 13-31) and 15 months (95%CI 8.0-22), respectively (*P*=0.019) and HR 2.0 (95%CI 1.1-3.5)). Survival for patients aged 75-79 receiving sCHRT was superior compared to ages 70-74 (HR 0.42 (95%CI 0.21-0.84)). The number of comorbid conditions was not associated with worse survival for both cCHRT and sCHRT. For RT and no curative treatment, none of the patient characteristics were associated with superior or worse survival. As >60% of patients had two or more mild, moderate or severe comorbid conditions, types of comorbidity were not included into multivariate analyses.



Number at risk

cCHRT	72	57	39	28	16	10	7
sCHRT	52	42	28	19	13	7	7
RT	34	22	16	8	6	5	3
No curative treatment	58	23	13	4	2	2	1

Figure 2. Kaplan-Meier survival curve and number at risk according to treatment group. Abbreviations: cCHRT 'concurrent chemoradiation', sCHRT 'sequential chemoradiation', RT 'radical radiotherapy'.

Table 3. Hazard Ratios (HRs) for predictors of survival stratified for cCHRT and sCHRT

	Predictor	Unadjusted HR (95%CI)	P-value	Adjusted HR (95%CI)	P-value
cCHRT	**Age**				
	70-74	*Reference*		*NA*	
	75-79	0.94 (0.50-1.8)	0.86		
	80+	1.7 (0.74-3.7)	0.22		
	WHO PS				
	0-1	*Reference*			
	2-3	1.6 (0.37-6.5)	0.55	*NA*	
	Comorbidity				
	No severe	*Reference*		*Reference*	
	Severe	2.0 (1.1-3.5)	0.024	2.1 (1.1-3.7)	0.017
sCHRT	**Age**				
	70-74	*Reference*		*Reference*	
	75-79	0.42 (0.2-0.84)	0.014	0.42 (0.2-0.84)	0.014
	80+	0.94 (0.44-2.0)	0.86	0.89 (0.41-1.9)	0.76
	WHO PS				
	0-1	*Reference*			
	2-3	0.91 (0.48-1.7)	0.78	*NA*	
	Comorbidity				
	No severe	*Reference*			
	Severe	0.76 (0.42-1.4)	0.35	*NA*	

Figures are displayed as HR (95%CI) 'Hazard Ratio (95% Confidence Interval)', abbreviations: cCHRT 'concurrent chemoradiation', sCHRT 'sequential chemoradiation', WHO PS 'World Health Organisation Performance Status', NA 'Not Applicable', HR>1.0 indicates worse survival, none of the unadjusted predictors was significant for radical radiotherapy or no curative treatment

Discussion

This study aimed to evaluate administered treatment, motives for omitting cCHRT and predictors for treatment tolerance and survival in unselected elderly patients with unresectable stage III NSCLC in daily clinical practice. The most common motives for omitting cCHRT were comorbidity and/or poor PS and patient refusal. Worse treatment tolerance and survival were found for severe comorbidity and survival was not significantly superior for cCHRT compared to sCHRT or RT.The proportion of patients receiving cCHRT (33%) was comparable to other elderly-specific studies (33-41%) [14, 22] and less often administered to patients aged ≥75 with PS ≥2 and severe comorbidity. Both PS and comorbidity are important indications for treatment toxicity and survival as reflected by the most common motives for omitting cCHRT and should be analyzed carefully before treatment decision-making [5, 7, 9, 21]. Not choosing intensive treatment could originate from cherishing a good QoL instead of longer survival time at the end of life [7, 11].

Toxicity rates are generally higher in unselected patients compared to selected patients in clinical trials [19]. PS, comorbidity and age could be predictors for treatment toxicity [32, 33]. Presumably, PS is a stronger and more robust risk factor than comorbidity due to assessment at diagnosis [7, 21]. However, ACE-27 can provide more detailed information to distinguish patients eligible for cCHRT or sCHRT due to a time window of events and severity of organ decompensation [17, 21, 29, 34]. In the present study, severe comorbidity (≥1 severe or ≥2 moderate decompensations) and ≥2 comorbid conditions indicated worse treatment tolerance for cCHRT and sCHRT (unplanned hospitalizations and/or not completing treatment). COPD (Chronic Obstructive Pulmonary Disease) is common among NSCLC-patients and can increase pulmonary toxicity when treated intensively [23]. Although the number of comorbid conditions is easier to use during clinical evaluation, investigating severity of comorbidity is preferable since it can be informative for both treatment tolerance and survival. Radiation esophagitis is common as well, especially for cCHRT, and may result in hospitalization, treatment interruption and worse treatment outcomes [35, 36]. Despite that hospitalizations were common for CHRT, the majority completed treatment as proper symptom management was applied. Radiotherapy technique can be related to treatment completion and tolerance [35, 36]. Despite of changes in techniques during this cohort, tolerance outcomes were not significantly different through included years (P=0.95). Since dose volume data for organs at risk were not available, it remains uncertain whether synergistic effects of comorbidity, organ dose volumes, radiation esophagitis and other adverse events decreased treatment tolerance in multimodality treatment [37-39].

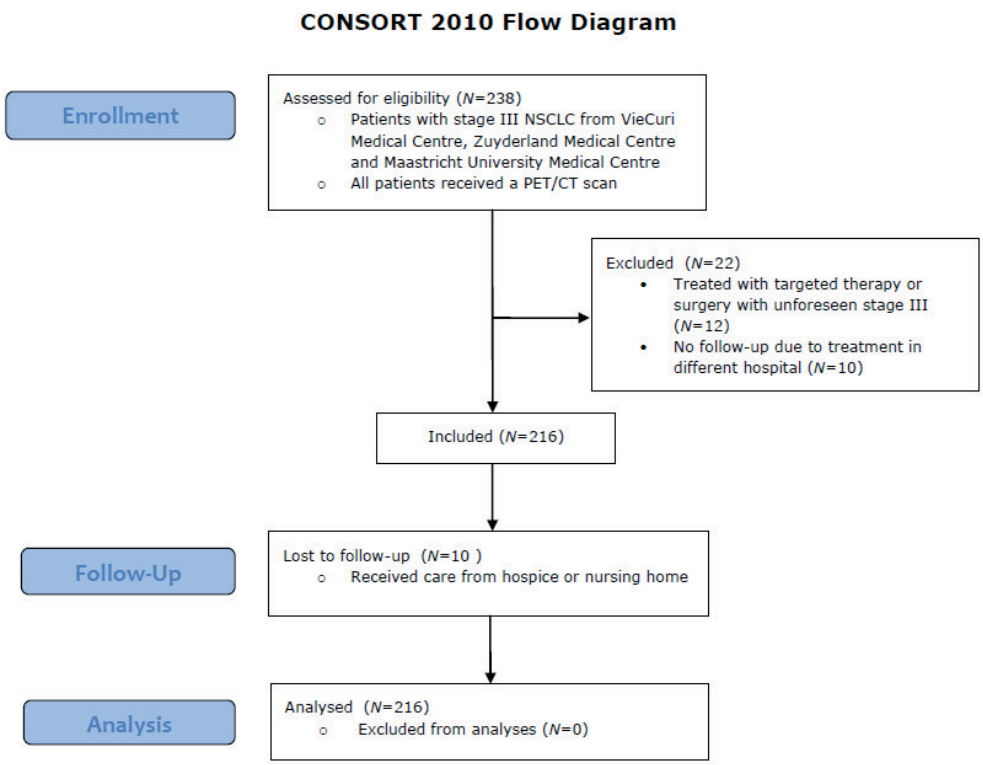
Median survival after cCHRT was not significantly superior compared to sCHRT or RT. This is in contrast to a meta-analysis and population-based study in which survival was superior for cCHRT compared to sCHRT. Although this might be explained by a lack of power in the current study, this could also be due to the fact that only younger patients and/or fit elderly were included which does not represent daily practice [1, 2]. Older patients are often treated less aggressive because of toxicity risk and potential worse survival [14, 15, 21]. On the contrary, patients aged 75-79 years receiving

sCHRT had better survival compared to ages 70-74. This is probably due to selection of the fittest elderly and can indicate that functional age instead of high age provides a broader view on possible treatment tolerance and survival [33]. PS was not found to be a significant predictor for survival in multivariate analyses. Scoring of PS is physician dependent and therefore could be more subjective. Also, correcting for two strongly related outcomes like PS and comorbidity in a multivariate model can lead to inclusion of the most explanatory only [21], which would be comorbidity in this case. In case of cCHRT, severe comorbidity was predictive for worse treatment tolerance and worse median survival compared to no severe comorbidity. The Raditux trial also found shorter survival in case of cCHRT and comorbidity and indicated the need for studies investigating (severe) comorbidity and treatment outcomes [23]. Possibly, worse survival for cCHRT could also be explained by poor-risk patients receiving carboplatin more often and higher survival rates can be reached in selected patients receiving cisplatin [40]. Due to minor differences in survival and less adverse events, it can be suggested that sCHRT is more feasible than cCHRT in unselected elderly [4] and RT remains an alternative for CHRT in patients with severe comorbidity [9, 10]. However, cCHRT should not be denied to selected elderly patients [14, 19, 41]. The strengths of our study are the high external validity and patient inclusion between 2009 and 2013. This provides fairly recent and demonstrative patient data which are generalizable to other unselected elderly NSCLC patients. Data quality and completeness was good since both medical files and the Netherlands Cancer Registry were used for retrieval. In addition, all patients were diagnosed and staged completely, including PET/CT. A weakness of this study is that due to the retrospective observational design, physicians selected the best suitable therapy for the patient and randomization has not been performed. However, analyses were stratified to take into account 'confounding by indication'. Some data regarding social factors were incomplete and could not be included in the analyses. A formal geriatric assessment is not included in standard care, and as such, we could not include extensive geriatric characteristics or a weighted geriatric score. An explanation for not detecting significant differences between curative options could be a lack of statistical power, as the number of patients required for detecting a significant and clinically meaningful difference for survival could not be included (>100 per treatment arm). Also, median FU was shorter for cCHRT (35 months) compared to sCHRT (62 months) and RT (47 months) and a relatively high proportion of patients receiving cCHRT was still alive at the end of the study period and censored. This might explain why long-term superiority of cCHRT over sCHRT for elderly could not yet be supported. Although this study was underpowered and conclusions should be drawn carefully, the negative impact of comorbidity on treatment tolerance and survival is potentially true.

Especially for the elderly, the goals and preferences of the patient regarding survival, QoL and tolerance of treatment are important to take into consideration in multidisciplinary decision-making. Consequently, there is a need for elderly-specific prospective observational studies addressing patient preferences, the role of severe comorbidity in treatment tolerance and survival and the probable survival benefit of cCHRT compared to both sCHRT and RT [10]. Comprehensive Geriatric Assessments (GCA) should be included to examine geriatric characteristics and QoL during and after treatment, in

order to provide a weighted score for geriatric characteristics to assess treatment outcomes and provide the best suitable treatment for each patient [13, 14, 33, 34]. These issues are largely addressed in the prospective randomized trial ELDAPT (NCT02284308), which has started recently in the Netherlands. The results of ELDAPT can facilitate treatment decision making since patient preferences and capacities can be collected more precisely and interpreted in the light of a geriatric view [7, 34].

In conclusion, comorbidity, poor PS and patient refusal were the most common motives for omitting cCHRT. Despite the fact that relatively fit and younger elderly were assigned to cCHRT, treatment tolerance was worse for patients receiving cCHRT, especially for those with severe comorbidity. Only minor differences in survival between cCHRT, sCHRT and RT were found. This means that sCHRT or RT might be more feasible treatment options for elderly. Future prospective studies should focus on patient preferences, (severe) comorbidity, predictive geriatric characteristics and include quality of life or functionality as important end points. As a result, more evidence can be gathered for treatment decisions in elderly patients with unresectable NSCLC, leading to the most optimal balance between quality of life and survival.



Supplemental figure 1. CONSORT flow diagram of the number of patients enrolled and analyzed in this retrospective observational study. Abbreviations: *N* 'number', NSCLC 'Non-Small Cell Lung Cancer', PET/CT 'Positron Emission Tomography - Computed Tomography'.

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Part 3

Optimizing treatment selection and outcomes

Chapter 8

Geriatric assessment for older patients with non-small cell lung cancer: daily practice of centers participating in the NVALT25-ELDAPT trial

Lung, aug 2018; 196(4):463-468

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Abstract

Introduction: Geriatric assessment (GA) for older patients with lung cancer could provide insight into vulnerability, cognitive impairment, and risk of toxicity. Discontinuation and complications of intensive treatment could potentially be prevented in vulnerable and frail patients. This study aimed to evaluate current clinical practice of GA for older patients with lung cancer in the Netherlands and identify potential hurdles for implementation.

Methods: Pulmonologists and radiation oncologists participating in the NVALT25-ELDAPT trial completed an online questionnaire regarding current practice of GA, added value of GA for treatment decision-making and logistic barriers for patients with non-small cell lung cancer.

Results: 15 out of 17 centers responded. Three performed GA as standard procedure, three on indication, eight considered a frailty screening step before GA, and one did not perform GA. Suspicion of cognitive problems was mentioned most often as indication for GA and of added value for treatment decision-making; followed by older age, curative-intent treatment, and stage I-III lung cancer. Administered instruments for screening and extensive GA were diverse. Main barriers to implement GA in clinical practice were logistic problems (timescales and availability of trained personnel).

Conclusion: The use of GA in clinical practice for patients with lung cancer varied widely across centers regarding instruments and domains. Physicians are uniform in their opinion about indications for GA and the added value for treatment decision-making. Research should focus on manageable instruments and important domains to assess for this heterogeneous group of older patients with lung cancer to optimize treatment selection.

Introduction

For older patients with cancer, geriatric assessment (GA) is recommended prior to treatment.[1, 2] Although evidence is accumulating, GA is considered time-consuming and not yet part of standard care.[1-3] However, it provides important information on multiple domains regarding age-related deteriorations (comorbidity, dependency and mobility, cognitive and emotional status, malnutrition and social context), and gains insight into patients' vulnerability.[4, 5] Half of patients with lung cancer are aged 70 years or older at the time of diagnosis.[6] Previously undiagnosed impairments come to light in 58% of this population through GA.[7] As a result, patients can receive non-oncologic interventions additional to treatment or adaptations in the intensity of treatment,[7] in order to avoid treatment-related toxicity.[8]

For patients with locally advanced (stage III) non-small cell lung cancer (NSCLC), a meta-analysis showed significant superior survival of concurrent chemoradiotherapy (CHRT) compared to sequential CHRT. However, patients aged 70 years or older were underrepresented (only 13% received concurrent CHRT and 19% sequential CHRT).[9]In the Netherlands, a retrospective study did not show superior survival for concurrent CHRT compared to sequential CHRT in patients aged ≥70 years in clinical practice,[10] and a nationwide study did not find significant differences in survival for CHRT between patients aged 65-74 years and those aged ≥75 years.[11] Also, complications, hospitalization, and discontinuation of treatment are common during CHRT, especially among older patients.[12-14] While better quality of life and functional status (IADL, Instrumental Activities of Daily Living) at diagnosis are associated with better prognosis among patients with advanced lung cancer undergoing chemotherapy,[15] half of patients with (locally) advanced NSCLC show functional decline during (intensive) treatment.[16] Therefore, it may be important to incorporate domains, which can be clarified by GA, in the process of treatment decision-making to estimate potential effects on treatment tolerance and survival.[17-19] Although advances in geriatric oncology and evidence regarding GA for patients with lung cancer are stacking, it remains unknown to what extent GA is currently applied in daily clinical practice.

The objective of this study was to evaluate the current practice of GA in the process of treatment decision-making in daily clinical practice and barriers for GA in standard care for older patients with lung cancer.

Methods

Pulmonologists and radiation oncologists of 17 treatment centers were approached to report on the use of GA in daily clinical practice in their hospitals by completing an online questionnaire. These physicians were principal investigators in the NVALT25-ELDAPT trial* (Elderly with locally advanced Lung cancer: Deciding through geriatric Assessment on the oPtimal Treatment strategy, study 25 of the Dutch association of medical specialists for lung disease and tuberculosis).

The online questionnaire was designed by consensus of the (co-)authors of this study (Appendix). SurveyMonkey (SurveyMonkey Inc., San Mateo, California USA, www.surveymonkey.com) was used for distribution and collection of answers between May and August 2016. The questionnaire addressed the assessment of older patients with (non-small cell) lung cancer in general clinical practice before initiation of the NVALT25-ELDAPT trial. Indications for GA, expected added value for treatment decision-making, instruments used to perform GA, potential barriers for the execution of GA in the context of the NVALT25-ELDAPT trial, and other relevant factors apart from GA (i.e. involvement of general practitioner (GP)) were included. The use of a GA was categorized as use of a screening step (to select a frail subpopulation in which GA is performed), an extensive multidomain assessment, or no assessment. Furthermore, the consultation of a geriatrician was assessed. A reminder was sent by email two weeks after non-response. The second reminder was sent two weeks thereafter, and the third reminder two weeks after the second. No further actions were issued in case of non-response after three reminders. IBM SPSS Statistics 22.0 was used for analysis. Results were displayed by frequencies, percentages, and expert opinion.

*The NVALT25-ELDAPT trial is registered under trial number NCT02284308. Details are available at www.eldapt.org (predominantly in Dutch). In the NVALT25-ELDAPT trial, all patients with stage III NSCLC aged 75 years or older will undergo extensive GA. Patients classified as vulnerable through GA are re-evaluated by a geriatrician and re-classified as fit (if applicable after geriatric intervention) or frail. Fit patients providing additional informed consent are randomized to concurrent CHRT or sequential CHRT, and frail patients receive treatment at the discretion of the pulmonologist. The aim of the NVALT25-ELDAPT trial is to generate evidence for predictive factors for quality-adjusted survival, GA instruments, and personalized treatment decision-making in this heterogeneous and under-investigated patient population. The results of the questionnaire stand apart from patient-related outcomes in the NVALT25-ELDAPT trial.

Results

Twelve pulmonologists and three radiation oncologists of 15 centers filled out the questionnaire with a total response rate of 88% (15/17). Sixty percent had ≥10 years of experience regarding treatment of lung cancer as a medical specialist. Extensive GA was standard procedure in three centers (20%, table 1), while GA was performed on indication in three additional centers.

Table 1 Applied information sources for standard evaluation of geriatric characteristics according to fifteen centers in current clinical practice

	A	B	C	D	E	F	G	H †	I	J	K	L	M	N	O
Pulmonologist	x	x	x	x		x	x	x		x			x		
General practitioner	x	x		x		x	x	x		x	x	x			
Geriatrician*	x	•	x	x	x						x	x			
Short screening	x	x	x		x	x									
Extensive screening	x	•		x	x			•							
No geriatric screening														x	

* consultation or presence at tumour board, † answered by radiation oncologist, x applied in current practice, • on indication

Of all physicians, 72% indicated that the clinical view of the pulmonologist was used to estimate geriatric factors. Also, 67% incorporated information from GPs, and only half of respondents included the view of a geriatrician (46%). Information provided by relatives was mentioned as well (13%). Most often, the view of the pulmonologist and GP were combined. In one center, no GA, screening instrument, or geriatric consultation was used in daily standard care. Reasons to perform geriatric screening in clinical practice were suspicion of cognitive problems (figure 1), followed by consideration of curative-intent treatment, age ≥70 years, stage I, II or III disease, and comorbidity. In two centers, age ≥70 years, and age ≥65 years were explicit and decisive indications to administer (extensive) GA as part of standard care. Predefined instruments contributing to GA were used in eight centers and ranged from one to seven domains, including instruments for performance status, comorbidity, mobility, and/or social environment (Table 2).

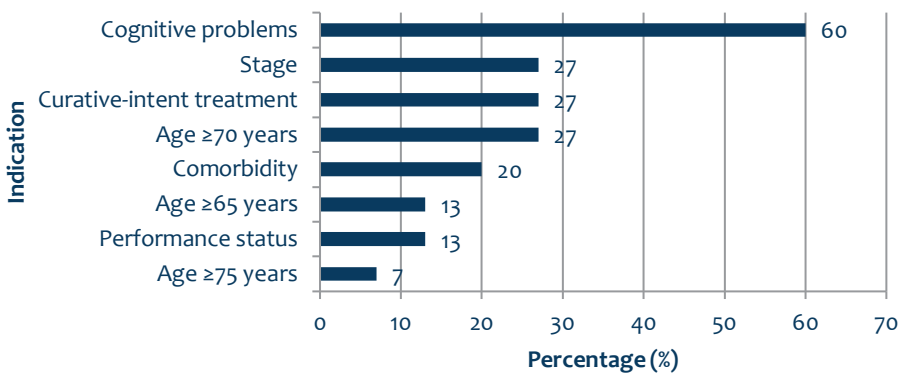

Figure 1. Indications for geriatric assessment according to fifteen centers. *Percentages are calculated for each indication individually (total count >100%)

Table 2 Components of short and extensive geriatric assessment indicated by six centers

Center	Screening instrument or tool	Geriatric assessment and its predefined components
A	G8	PS, comorbidities, mobility, social environment
B	Components unknown	Geriatric navigator, MMSE, MNA, PS, comorbidity, mobility, social environment
C	SPPB	Geriatric navigator
D	Extensive screening only	ADL, IADL, MNA, PS, comorbidities, mobility, social environment
E	GFI	On indication, components unknown
F	ICF	On indication, components unknown

Abbreviations: 'PS' performance status, 'SPPB' short physical performance battery, 'GFI' Groningen frailty indicator, 'ICF' international classification of functioning, 'MMSE' mini-mental state examination, 'MNA' mini nutritional assessment, 'ADL' activities of daily living, 'IADL' incremental activities of daily living

Although GA was not part of standard care in most centers, several indications were recognized to be important for treatment decision-making (figure 2): Suspicion of cognitive problems, consideration of treatment with curative intent, multiple comorbidities, stage III disease, and performance status (score ≥2 according to 47% of respondents). One respondent explicitly mentioned that any physical performance score could lead to additional GA, as it is a subjective measurement. Another respondent designated that performance score is only a limited estimation and should not influence the application of GA. Additionally, the following results of the GA were broadly recognized to adjust treatment regimen: dementia, ADL-dependency, vulnerability, no caretakers, and malnutrition (figure 3). One respondent explicitly indicated that only a complete GA would be important to deviate from standard treatment and not individual deviant domains.

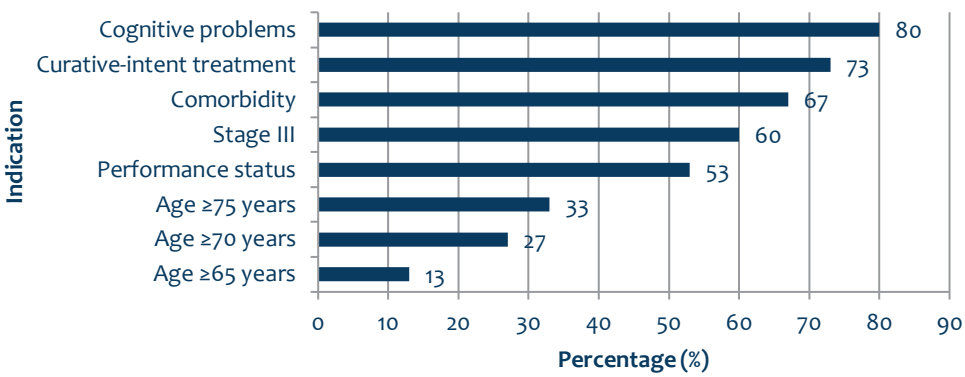

Figure 2 Indications for which geriatric assessment could provide added value according to fifteen centers. *Percentages are calculated for each indication individually (total count >100%)

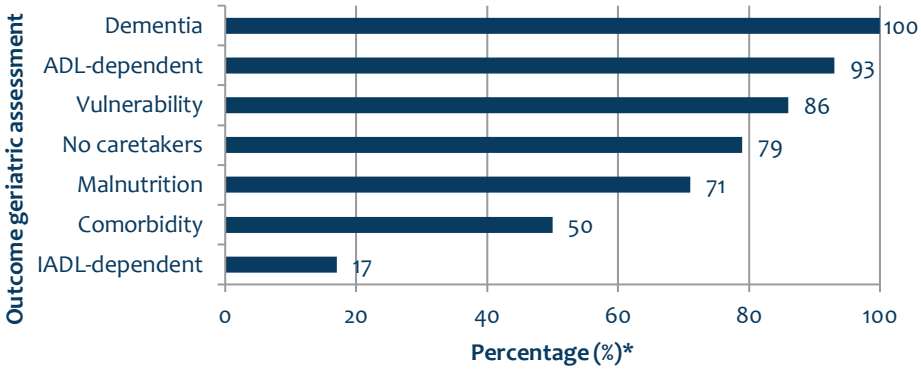

Figure 3 Important outcomes of geriatric assessment to deviate from standard treatment according to fourteen centers. Abbreviations**:** ADL 'Activities of Daily Living', IADL 'Instrumental Activities of Daily Living'. *Percentages are calculated for each indication individually (total count >100%)

Barriers that were considered to hinder the execution of GA in current clinical practice were logistic planning within hospital timescales (53%), availability of a geriatrician (40%), staff planning and budget (33%), and patient motivation (27%). Only three centers did not mention barriers (20%): Two of these three centers already incorporated GA as part of standard care and the third performed GA on indication. All participants acknowledged the need for scientific evidence in this field.

Discussion

The use of GA in standard daily care for older patients with lung cancer varied widely among treatment centers in the Netherlands. Everyday sources for (geriatric) information were dissimilar, as were instruments for a screening step, and for extensive GA covering different domains. Especially (suspicion of) cognitive problems were recognized to be of added value for treatment decision-making, followed by older age, intention to start curative treatment, and stage I-III NSCLC.

The added value of GA in older patients with cancer has been widely recognized in the research field of geriatric oncology.[1] Current evidence mainly focused on geriatric patients with breast or colorectal cancer, with less evidence for the heterogeneous and often vulnerable group of patients with lung cancer. Suspicion of cognitive problems, curative-intent treatment, and higher age are recognized as important indications for GA as they could impact treatment tolerance, survival, and quality of life.[12, 17] High age alone should not be decisive to withhold standard treatment. Although age-related deteriorations are warranted in this group, they are not visible or estimable without GA.[7, 20] Consequently, clinical judgments of PS or comorbidity by the treating physician could result in less intensive treatment, while specific advice of a geriatrician is lacking.[16]

Specific indications for GA were acknowledged more often than the actual application of these indications in clinical practice, which may reduce the impact on treatment decision-making and treatment outcomes.[21] This discrepancy could be due to several barriers like lack of consensus on the gold standard of GA, lack of standards to classify patients into risk groups,[21] lack of evidence regarding the effectiveness of GA for this specific patient group,[4] or logistic issues withholding cooperation with a geriatrician. In this study, logistic issues were mentioned most often, such as timescale for diagnostic procedures and decision-making, as well as the availability of a geriatrician. Over half of centers indicated that treatment decision-making for older patients with NSCLC was based on the clinical view of the treating physician, without interference of a geriatrician. It is known that the evaluation of geriatric characteristics by physicians other than geriatricians can lead to misclassification of frailty in older patients with cancer.[22] Although information of the GP may provide additional insights in overall health status of the patient, essential information may be overlooked, leading to an underestimation of pre-frailty and frailty.[18, 20] Numerous actual health problems can only be discovered by thorough assessment, which could alter treatment decisions in at least one in four patients.[7, 20, 21] Unrecognized deficits and strengths may influence treatment decisions and, consequently may negatively impact treatment outcomes and quality of life.[4, 15] Therefore, implementation projects for uniform, reliable, and clinically applicable GA are necessary and should be facilitated on an (inter)national level.[2]

Screening instruments are often used before applying more extensive GA as the use is less time-consuming, cumbersome, and resource-intensive.[20, 23] However, a large variety of screening instruments are used.[17, 24] Systematic evidence pointed out that the effectiveness of screening instruments remains equipoise and the superiority of a specific tool could not be affirmed due to diverse applications in trials and clinical practice.[5, 21] Nonetheless, at least some form of GA should be considered to personalize treatment decision-making.[18] Additional specific instruments, such as the CARG or CRASH toxicity tools can be considered to gain insight in a specific outcome, i.e. predicting (treatment-related) toxicity.[25, 26] Nevertheless, the processing times within the hospital could delay the start of treatment, as well as the logistic planning, costs, and time consumption of planning and performing GA.[20, 21] Although these barriers for extensive GA are broadly recognized, these are not easy to overcome in clinical practice. Therefore, evidence regarding GA for patients with lung cancer specifically is highly needed. The recently started NVALT25-ELDAPT trial aims to generate evidence regarding screening instruments, extensive GA, cut-off points for vulnerability, and evidence regarding survival, toxicity, and quality of life for the heterogeneous and predominantly older group of patients with stage III NSCLC.[4, 21] As the available evidence is scarce for this understudied group, the results of the trial are awaited expectantly to improve treatment-decision-making by guidance of GA in the future and thereby optimizing patient-centered outcomes.

The high response rate and results of this study confirm the importance and need for evidence of GA for older patients with NSCLC. As principal investigators of the centers participating in the NVALT25-ELDAPT trial were approached before initiation of the

study, outcomes could be incorporated directly into logistic information and prevent possible barriers of the study program. An additional evaluation will be performed after implementation of the trial in the same centers, examining experiences and barriers of extensive geriatric screening. Other strengths are that abundant and specific information could be collected in a short period of time by distributing a questionnaire. A limitation of the study is that a validated questionnaire was not available. However, it was designed by consensus of the project leaders and face validity has been extensively evaluated. Also, the content and intention of questions were independently evaluated and thoroughly discussed afterwards by a radiation oncologist, pulmonologist, and two (clinical) epidemiologists. This leads to highly specific and relevant questions for the objective of this study, and effects of researcher imposition were minimal.[27] Another potential limitation is that the rather small sample size might have led to selection bias, as included centers could be more research-minded compared to other clinical facilities in the Netherlands and Belgium. However, principal investigators were selected before initiation of the trial and regarded as representatives for their multidisciplinary team of academic, teaching, and tertiary centers. Hereby, valuable insights could be gained regarding the current practice of GA for patients with lung cancer covering fifteen different centers.

Conclusion

The use of GA varied widely across centers treating older patients with lung cancer. Logistic barriers as timescales and availability of a geriatrician seem to be dominant for implementing GA in standard care. Although physicians recognize patient categories that could benefit from GA and factors which are of added value for treatment decision-making, specific evidence regarding tools and individual patients is highly needed in order to select the optimal treatment strategy in this older and heterogeneous patient group. The current results set priority for properly conducted research to determine the effectiveness of GA, specific domains, and tools to assess vulnerability correctly among older patients with NSCLC.

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Chapter 9

Effects of prehabilitation and rehabilitation including a home-based component on physical fitness, adherence, treatment tolerance, and recovery in patients with non-small cell lung cancer: a systematic review

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Abstract

This systematic review aimed to examine physical fitness, adherence, treatment tolerance, and recovery for (p)rehabilitation including a home-based component for patients with non-small cell lung cancer (NSCLC). PRISMA and Cochrane guidelines were followed. Studies describing (home-based) prehabilitation or rehabilitation in patients with NSCLC were included from four databases (January 2000-April 2016, N=11). Nine of ten rehabilitation studies and one prehabilitation study (437 NSCLC patients, mean age 59-72 years) showed significantly or clinically relevant improved physical fitness. Three (27%) assessed home-based training and eight (73%) combined training at home, inhospital (intramural) and/or at the physiotherapy practice/department (extramural). Six (55%) applied supervision of home-based components, and four (36%) a personalized training program. Adherence varied strongly (9-125% for exercises, 50-100% for patients). Treatment tolerance and recovery were heterogeneously reported. Although promising results of (p)rehabilitation for improving physical fitness were found (especially in case of supervision and personalization), adequately powered studies for home-based (p)rehabilitation are needed.

Introduction

Non-small cell lung cancer (NSCLC) concerns 85% of all lung cancer patients.[1] Five-year survival rates remain low ranging from 55%, 41%, 13%, to 2% for stage I, II, III and IV, respectively.[2] Standard curative treatments, including lung resection[3] and concurrent chemoradiation,[4] lead to adverse events in ≥50% of patients and frequently require hospitalization.[5, 6] High age,[7] smoking-related comorbidities, frailty, poor performance status, and long-term physical inactivity are often present in patients with NSCLC.[5, 8-10] These characteristics may affect mobility, independence, treatment tolerance, recovery, and prognosis.[11-15] Resistance and endurance training can increase the functional and physiological reserve, thereby creating a safety margin to meet potential enlarged demands of cardiac output and other physical capacities at the time of disease and interventions.[15, 16] Prehabilitation (therapeutic training before undergoing treatment)[16] and rehabilitation (therapeutic training during and after treatment)[17] can optimize physical fitness, treatment tolerance, recovery, and survival,[18-20] even in older cancer patients.[21-23] However, intramural training (inhospital) or extramural training (at the physiotherapy practice or department) may counteract compliance of high-risk patients because of commuting problems, accessibility of services, multimorbidity, and vulnerability.[24, 25] A personalized training program in a home-based setting might overcome these barriers and enhance both motivation and adherence, especially for vulnerable and older patients.[20] Therefore, the aim of this study is to systematically review the literature regarding feasibility and effectiveness of prehabilitation and rehabilitation including a home-based component in patients with NSCLC by evaluating physical fitness, and to describe adherence and treatment tolerance, and recovery.

Methods

The Cochrane guidelines for systematic reviews[26] and PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[27] were followed. Databases Pubmed, Medline, Embase, and PEDro were searched for eligible articles describing patients with NSCLC undergoing prehabilitation or rehabilitation including a home-based component focusing on physical fitness (Table 1). Search terms were explored on free text words to avoid exclusion of recently published articles. Inclusion was limited to studies in English or Dutch language between January 1, 2000 and April 11, 2016. The primary outcome was physical fitness and secondary outcomes were patient adherence, exercise adherence, treatment tolerance, and recovery. Studies were excluded when insufficient training information was available to distinguish prehabilitation and rehabilitation, and when no physical intervention was applied.

Study selection

All search results were combined and duplicates removed. Assessment of title, abstract and full-texts according to eligibility criteria was performed independently by reviewers MP and ED. Inclusion of eligible studies was discussed until consensus. If no consensus was reached, a third person (BB) determined eligibility. Studies were included when full-text was available. Reference tracking was performed after full-text assessment in order to include additional relevant studies.

Data collection process and items

For each included article, the following information was independently collected, compared, and combined: first author, publication year, study type (prehabilitation/rehabilitation, country, type of study, randomization), demographics (number of patients with NSCLC, stage of disease, age, sex, treatment, comorbidity, performance status), description of the intervention (exercise content, frequency, intensity, measurement times, exercise time, follow-up, time of delivery, controls), and outcomes (physical fitness, patient adherence, exercise adherence, treatment tolerance, recovery). Physical exercises consisted of resistance and endurance training, and training effects were mainly evaluated by the 6-minute walk test (6MWT) distance). Results were described as mean ± standard deviation, mean (range), or mean difference ± standard deviation. A minimal clinically important gain of ≥42 meters or 9.5% change was considered clinically relevant for 6MWT distance.[28] Patient adherence was described; both patient and exercise adherence (percentage) were considered sufficient above 70%. Treatment tolerance and recovery were displayed by adverse events (numbers, including postoperative complications) and hospitalization time (days, mean ± standard deviation). Differences between outcomes were considered statistically significant if $P<0.05$.

Table 1. Combinations of text words per database of the literature search

Databases	Population Non-small cell lung cancer	Intervention Home-based (p)rehabilitation	Outcome Physical fitness
Embase, Pubmed, Medline*	(Non-small cell lung cancer OR NSCLC OR lung cancer) **AND** (patient OR geriatric OR elderly OR aged OR high-risk OR vulnerable OR frail) **NOT** (children OR caregiver OR tuberculosis OR aneurysm)	(prehabilitation OR before OR prior to OR presurgical OR preoperative OR during OR undergoing OR rehabilitation OR perioperative OR following OR postoperative OR lung resection OR lobectomy OR physical therapy OR training OR exercise OR physiotherapy OR physical therapy modality) **AND** (home-based OR living environment OR outpatient OR home OR home-based intervention) **NOT** (costs OR lung cancer screening OR drug-reimbursement OR homeopathy OR oxygen OR video-assisted)	(Physical activity OR fitness OR physical function OR functional status OR ADL OR strength OR resistance OR physical endurance) **NOT** (Genetic OR genomic OR gene OR radon OR air pollution OR asbestos OR cell dynamics OR drug-resistance OR smoking)
PEDro*	Lung cancer	Exercise** **AND** home**	

* Free text words were applied to all search terms; filters were applied to language (English and Dutch included) and publication date (Jan-1-2000 until Apr-11-2016 included); Search terms for population, intervention and outcome were all combined by 'AND'. ** Truncation of search terms

Qualitative and quantitative assessment

Methodological quality was independently assessed by using the domain-based evaluation for systematic reviews by the Cochrane 'Risk of bias tool'.[29] Selection-, performance-, detection-, attrition-, and reporting bias were scored present (+) or absent (-). Low, moderate, or high risk of bias was determined by the percentage of present bias, corresponding to high (≤17%), moderate (18-33%), or low (≥50%) methodological quality, respectively. Therapeutic validity for quality of the training content was assessed by the CONTENT scale (Consensus on Therapeutic Exercise Training).[30, 31] Nine items regarding patient eligibility, competences and setting, rationale of the study, content of the study, and adherence were scored as performed (+) or not performed (-), where ≥6 times 'performed' indicated high therapeutic validity. The interobserver agreement was calculated by Cohen's Kappa, with poor (<0.20), reasonable (0.21-0.40), moderate (0.41-0.60), good (0.61-0.80) or very good (>0.80) agreement.[32] A meta-analysis could not be performed due to clinical and statistical heterogeneity in patient samples, exercise design, study execution, and reporting of physical outcomes.

Results

The literature search identified 141 hits, leading to 107 unique studies of which 74 did not meet inclusion criteria. Thirty-three studies were selected for full-text assessment and 24 of them were excluded (conference paper with no available full-text version, *n*=16), no physical outcome (*n*=3), no home-based intervention (*n*=2) or other reasons (*n*=3)). Reference tracking identified two additional articles. Eventually, 11 studies were included.[33-43] The PRISMA flow diagram is shown in Figure 1.[27]

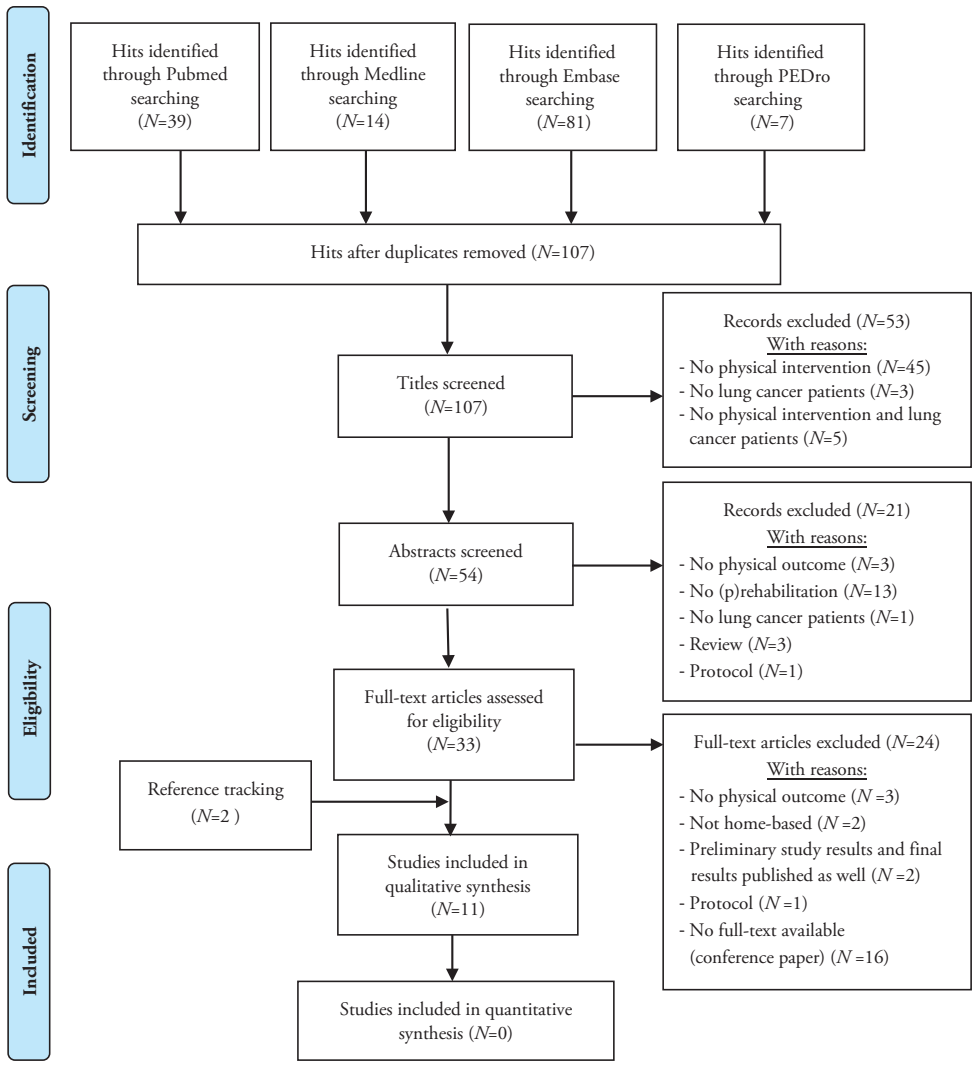

Figure 1. PRISMA Flow diagram displaying the selection of studies and reasons for exclusion

Study characteristics

Fourhundred-fiftyone lung cancer patients were included (97% NSCLC) with various stages of disease and treatment regimens. Ranges for sample size and mean age were 5-131 participants and 59-72 years, respectively. In Table 2, characteristics of included studies are displayed.

Only one study described prehabilitation[39] and ten studies described rehabilitation.[33-38, 40-43] Home-based training alone was examined in three studies (27%).[38, 39, 41] One study (9%) combined home-based and extramural training,[37] six studies (55%) combined home-based and intramural training,[33-36, 42, 43] and one study (9%) combined all three.[40] The intervention period lasted four to 16 weeks. The home-based training component mainly consisted of resistance exercises (muscle strength) and endurance exercises (cardiorespiratory fitness),[35, 37-42] or mere walking.[33, 34, 36, 43] Only four interventions (36%) were personalized.[34, 35, 40, 41] Supervision was performed by telephone calls,[36, 38-42] home visits,[36, 40, 41] or during intramural sessions.[33, 34, 36, 37, 42, 43] The number of home-based training sessions varied between twice a week[37, 38] and once a day,[34, 36, 37, 40] and moderate intensity was mainly applied. Intramural and extramural training consisted of supervised endurance training combined with resistance exercises. The number of sessions varied from twice a day postoperatively[35, 40] to once a week,[37] from 10-30 minutes[40] up to 1.5 hour[33, 34] at moderate or high intensity. These sessions took place during hospitalization after surgery followed by home-based training alone,[35-37] intramural training combined with concurrent home-based exercises,[33, 42, 43] or intramural training with home-based exercises in between.[34, 40] Five studies (45%) included a control group that received regular care,[35, 36, 40] home-based exercises,[37] or no exercises.[38]

Physical fitness was mainly measured by cardiorespiratory fitness (6MWT distance)[35, 37, 39-43] and muscle strength (kilogram of resistance per muscle group).[35, 36, 39, 42, 43] All studies (100%) reported patient adherence (percentage) and most described reasons for drop-out. Six studies (55%) reported on compliance of home-based exercises (percentage).[37, 38, 40-43] Treatment tolerance and recovery were described as adverse events (including post-operative pulmonary complications),[38, 39] or hospitalization days.[35-37, 40, 41] Other results of physical outcomes are displayed according to measuring instruments in Table 3[44-50].

Results of individual studies

The prehabilitation study and six rehabilitation studies (64%) described significantly improved physical fitness after (home-based) training.[33, 35, 39, 40, 42, 43] Three additional rehabilitation studies (27%) indicated improved physical fitness as well, although significance was not reported.[37, 38, 41] Specific outcomes are displayed in Table 2. The 6MWT distance was described in seven studies (64%), including the prehabilitation study, and showed a significant improvement of 28 to 65 meters (5.2%-43%).[35, 37, 39-43] In five of them, this gain was clinically relevant.[35, 37, 40-42] Muscle strength increased significantly during training sessions for most muscle groups.[36, 39, 42, 43] All studies described patient adherence and varied from 50%[42] to 100%[39, 41]. Main reasons for dropout were clinical deterioration, incomplete data-assessment, dying, and withdrawal from study-protocol. In all three studies examining home-based training alone, patient adherence was sufficient (72%, 100%, and 100%, respectively).[38, 39, 41] In three of eight studies combining home-based with extramural and/or intramural training, patient adherence was sufficient (71%, 72%, and 79%, respectively), [33, 37, 43] and varied from 50-68% in the remaining five studies.[34-36, 40, 42] Reported exercise adherence for the home-based component varied from 9%[43] to 125%[39] and was sufficient in four of six studies.[38, 39, 41, 42] Six studies included adverse events or hospitalization time (55%). For surgical patients, hospitalization varied in the intervention group from four[40] to nine days,[37] compared to six[40] to eleven days[35] in the control group. Adverse events were absent[39, 43] or occurred infrequently during the postoperative period.[35]

Table 2. Description of demographics and results of included (home-based) (p)rehabilitation studies

First author, year	Study type 1(P) rehabilitation 2. Country 3. Type of study 4. Randomization	Demographics (IG/CG)	Intervention exercise (IG/CG)	Intervention 1. Measurement times 2. Exercise time (min) 3. Follow-up 4. Delivery	Outcomes (IG/CG) 1. Physical fitness 2. Patient adherence (drop-out) Exercise adherence (compliance) 3. Treatment tolerance and recovery
Andersen 2011	1. Rehabilitation 2. Denmark 3. PCT 4. NA	N=24 **NSCLC** N=19 **Age** mean (range) Men 64(55-77) Women 67(48-76) **Treatment** N Surgery 5, CT 19,RT 8,TKI1	**Home-based** 5/wk for 7 weeks unsupervised diary-based aerobic (walking) + breathing **Intramural (simultaneously)** 2/wk for 7 weeks supervised group sessions, aerobic (walking (85% VO2max)) + breathing **Control** NA	1. T0 1st supervised training T1 last supervised training 2. Home training NR; Intramural 90 3. Wk1-10/11 4. After surgery; during CT, RT, or TKI	1. ISWT med diff (range) +9% (-77; 39%) P=0,021 ESWT med diff (range) +109% (-70;432%) P=0,002 FEV1 med diff (range) 0% (-0,3;0,6%) P=NR 2. **Drop-out** with reasons (N) home-based NR; intramural 29%, <65% of sessions present (3), incomplete data ISWT (4) **Compliance** (N) NR; continued after intervention (7) 3. NR
Andersen 2013	1. Rehabilitation 2. Denmark 3. PCT 4. NA	N=51 **NSCLC** N=39 **Age** mean ±SD Men 65±8, women 65±7 **Treatment** N Surgery 10, CT 26, RT 3, TKI 2	**Intramural** 2/wk for 3 weeks aerobic (cycling and walking (Borg RPE 16-18)) + breathing Repetition of this design after home training **Home-based** 7/wk for 3 weeks (between intramural sessions) personalized unsupervised diary instructed aerobic + breathing **Intramural** 2/wk for 3 weeks intramural regimen **Control** NA	1. T0 1st supervised training T1 last supervised training 2. Home training NR; Intramural 90 3. Wk1-13 4. Unclear (after surgery; during or after CT, RT, and TKI	1. VO2max (ml/O2/kg/min) mean±SD T0 14±3 T1 14±3 P=0,763 FEV1 (L) mean±SD T0 2,0±0,6 T1 2,0±0,5 P=NS 2. **Drop-out** with reasons (N) 43%, withdrawal after first session (7), withdrawal after home sessions (9), <65% present at second session (6); After intervention, not continuing physical activity (8), LFU (3) **Compliance** (N) NR; continued after intervention (18) 3. NR

Table 2: continued

First author, year	Study type 1(P) rehabilitation 2. Country 3. Type of study 4. Randomization	Demographics (IG/CG)	Intervention exercise (IG/CG)	Intervention 1. Measurement times 2. Exercise time (min) 3. Follow-up 4. Delivery	Outcomes (IG/CG) 1. Physical fitness 2. Patient adherence (drop-out) Exercise adherence (compliance) 3. Treatment tolerance and recovery
Arbane 2011	1. Rehabilitation 2. UK 3. RCT 4. Block randomization N=26/25 **NSCLC** N=26/25 **Stage** N I 15/10, II 6/6, III 2/0, IV 0/5, NR 3/4 **Age** mean (range) 62,6(32-47)/65,4(47-82) **Sex** NR **Treatment** N Surgery 26/25	**Intramural** 2/day for 5 days postoperative mobility + resistance (seated leg raises) + aerobic (walking, cycling 60-80% HRx) **Home-based** 12 weeks personalized (based on hobbies) aerobic (walking) + strength (not specified) with monthly supervision/home visit **Control** Monthly check-up calls and usual care including breathing + mobilisation		1. T0 preoperative T1 postoperative day5 T2 postoperative wk12 2. NR 3. Preoperative-postoperative wk12 4. After surgery	1. 6MWT (m) mean±SD T0 466,6±102,1 / 455,7±98,0; T1 336,7 ±84,1 / 308,7± 124,8; T2 480,2±110,0 / 448,2±95,1 P=0,89§; P<0,00† Quads strenght (kg) mean±SD T0 33,2±15,2 / 29,1± 10,9; T1 37,6± 27,1 / 21,5± 7,7; T2 34,2± 9,4 / 26,4± 9,7; P=0,04*; P=0.70† 2. **Drop-out** with reasons (N) 15%/32%, IG: palliative care (1), no surgery (1), refused measurement (1), no reason (1); CG: ITU admission (1), no reason (1), palliative care (1) withdrawal (1), refused (3) **Compliance** (N) NR 3. Length of hospital stay (days) mean±SD 8,9±3,3 / 11,0±8,9 P=NR ; A priori post-operative complications (N) 2/3 P=NR

Table 2: continued

First author, year	Study type 1(P) rehabilitation 2. Country 3. Type of study 4. Randomization	Demographics (IG/CG)	Intervention exercise (IG/CG)	Intervention 1. Measurement times 2. Exercise time (min) 3. Follow-up 4. Delivery	Outcomes (IG/CG) 1. Physical fitness 2. Patient adherence (drop-out) Exercise adherence (compliance) 3. Treatment tolerance and recovery
Arbane 2014	1. Rehabilitation 2. UK 3. RCT 4. Online randomization	N= 64/67 **NSCLC** N= 64/67 **Stage** N I 24/29, II 12/12, III 6/8, IV 7/2, NR 15/16 **Age** mean±SD 67±11/68± 11 **Sex** N(%) female 35(55)/24(36) **Treatment** N Surgery 64/67 **Comorbidities** N(%) COPD 34(53)/29(43)	**Intramural** 1/day for 5 days postoperative supervised strength (ankle lift (10-RM)) + aerobic (cycling (max 60% heart rate reserve), intensity increases daily **Home-based** 7/wk for 4 weeks unsupervised walking by pedometer and weekly calls **Control** Monthly check-up calls and usual care including pain relief by breathing and mobilisation exercises	1. T0 preoperative T1 postoperative day5 T2 postoperative wk4 2. Home training 30 Intramural 30 3. Preoperative-postoperative wk4 4. After surgery	1. ISWT (m) med(IQR) T0 290(180-440)/290(200-450); T1 110(NR) /135(NR); T2 350(NR)/290(NR); P>0,05‡; P>0,05§ Quads strength (kg) mean change diff(95%BI) T2 4,7(0,18-0,20); P=0,04‡ in COPD patients 2. **Drop-out** with reasons (N) 38%/43% IG: inoperable (3), no cancer (6), ITU admission (4), withdrawal (6), moved (1), rehospitalized (1), deceased (1), failed activity monitor (2); CG: inoperable (4), no cancer (1), no NSCLC (2), deceased (4), ITU admission (9), refusal (1), withdrawal (2), additional surgery (1), moved (1), failed activity monitor (4) **Compliance** (N) NR 3. Length of hospital stay (days) mean(range) 7,5(5-8)/7,1(6-8) P>0,05‡ A priori postoperative complications (n(%)) 20(31) / 22(33) P=NR

Table 2: continued

First author, year	Study type 1(P) rehabilitation 2. Country 3. Type of study 4. Randomization	Demographics (IG/CG)	Intervention exercise (IG/CG)	Intervention 1. Measurement times 2. Exercise time (min) 3. Follow-up 4. Delivery	Outcomes (IG/CG) 1. Physical fitness 2. Patient adherence (drop-out) Exercise adherence (compliance) 3. Treatment tolerance and recovery
Brocki 2014	1. Rehabilitation 2. Denmark 3. RCT 4. Computer-generated randomization tables	N=39/39 **NSCLC** N= 39/36 **Stage** N I 16/10, II 17/14, III 4/7, unknown 2/15 **Age** mean±SD 64±10/65± 9 **Sex** N(%) female 19(46)/13(35) **Treatment** N Surgery 41/37 **Comorbidities** N COPD 8/5, DM 5/3, CVD 8/12, previous malignancy 12/13	**Extramural** 1/wk for 10 weeks starting wk3 postoperative supervised group aerobic (walking with increasing intensity) + strength + breathing **Home-based (simultaneously)** 2/wk strength + 7/wk aerobic (walking, cycling (BORG RPE 11-12)) diary based; wk3-4months postoperative **Control** 2/wk strength + 7/wk aerobic (walking, cycling (BORG RPE 11-12)) diary based at home	1. T0 postoperative wk3 T1 4 months after baseline T2 1 year after baseline 2. Home training 30 Extramural 60 3. Baseline-12months after baseline 4. After surgery	1. 6MWT (m) mean±SD T0 427±124 / 407± 102; T1 mean diff baseline 61± 52 / 55± 45 P=0,57‡ T2 mean diff baseline 65± 70 / 60±45 P=0,93‡ FEV1 (L) mean±SD T0 1,73±0,5 / 1,9± 0,6; T1 mean diff baseline 0,14± 0,3 / 0,1± 0,4 P=0,84‡ T2 mean diff baseline 0,1± 0,4 / 0,06± 0,4 P=0,84‡ 2. **Drop-out** with reasons (N) 28%/14% IG: deceased (3), withdrawal (8); CG: deceased (2), withdrawal (3) **Compliance** Home-based (IG/CG %) 43%/14%; extramural (IG N) 17 in 10 sessions, 8 in 9, 5 in 8 and 2 in 6-7 sessions 3. Length of hospital stay (days) mean±SD 9±5 / 10±5 P=NR
Cheville 2013	1. Rehabiliation 2. United States 3. RCT 4. Unblinded block randomization	N=26/33 **Lung cancer** N=16/18 **Stage** N IV 26/33 **Age** mean±SD 63,8±12,5/65,5±8,9 **Sex** N(%) female 17(51,5) /14(42,4) **Treatment** N (NR 5/4) RT 4/4, CT 24/25	**Home-based** 2/wk for 8 weeks strength (Borg CR10) + 4/wk for 8 weeks aerobic (walking, 1 mile/20 min) diary based and every two weeks check-up calls **Control** No exercises or monitoring during intervention period	1. T0 wk1 T1 wk8 2. Home training 20 3. Baseline-12 months 4. During (palliative) treatment	1. Mobility mean diff±SD 4,88(4,66)/0,23(5,22) P=0,002 Activity mean diff±SD 1,56±5,53/0,94± 5,91 P=0,74 Steps/day (N) mean T0 3200/NR; T1 4400/NR ; P=NR *Self-reported Ambulatory Post Acute Care Daily Activities Short Form 2. **Drop-out** with reasons (N) 27%/9% IG: deceased (5), LFU (1), fracture (1); CG: deceased (2), LFU (1) **Compliance** (N) IG: 26, 77% 3. No adverse events during home-based program, difference deceased participants IG/CG NS

Table 2: continued

First author, year	Study type 1(P) rehabilitation 2. Country 3. Type of study 4. Randomization	Demographics (IG/CG)	Intervention exercise (IG/CG)	Intervention 1. Measurement times 2. Exercise time (min) 3. Follow-up 4. Delivery	Outcomes (IG/CG) 1. Physical fitness 2. Patient adherence (drop-out) Exercise adherence (compliance) 3. Treatment tolerance and recovery
Coats 2013	1. Prehabilitation 2. Canada 3. PCT 4. NA	N=13 **NSCLC** N=13 **Stage** N I 5, II 4, III 0, IV 2 **Age** mean±SD 59±9 **Sex** N female 5 **Treatment** N Awaiting surgery 10, CT 1, CT palliative 1, RT+CT palliative 1 **Comorbidities** N COPD 5, hypertension 5, dyslipidemia 3, DMII 2, anxiety 2	**Home-based** 3-5/wk for 4 weeks diary based aerobic (cycling (Borg BS≥6)) + strength and weekly check-up calls **Control** NA	1. T0 baseline T1 wk4 2. Home training 30 3. Wk1-4 4. Before treatment	1. VO2max (mL/kg/min) mean±SD T0 21,6±7,8; T1 23,3±7,5 P>0,05 VO2max (L/min) mean±SD T0 1,63±7,8; T1 1,75± 0,71 P>0,05 CWCE (s) mean±SD T0 264± 79; T1 421± 241 P<0,05 6MWT(m) mean±SD T0 540±98; T1 568±101 P<0,05 Muscle strength (kg) mean increase (SD); %±SD m. deltoideus: 1,82±2,83; 18±31; P<0,05; m. triceps: 1,32±1,75; 14±25; P<0,05; m. hamstrings: 3,41±3,7; 27±40; P<0,05; Handgrip, m. biceps and m. quadriceps NS 2. **Drop-out** with reasons (N) 0% **Compliance** (%) Aerobic (125); strength (84); recruitment (50) 3. No adverse events
Granger 2013	1. Rehabilitation 2. Australia 3. RCT 4. Computer-generated randomization tables	N= 7/8 **NSCLC** N=2/5 **Age** mean±SD 57±16,2/72.4±12,4 **Sex** % female 57,1/37,5 **Treatment** N Surgery 7/8	**Intramural** From postoperative until discharge aerobic (walking (Borg BS 4) 2/day, cycling 1/day) + strength (Borg RPE 13) 1/day)) **Home-based** 7/wk for 2 weeks after discharge personalized aerobic (walking (Borg BS 4)) + strength 1/wk check-up calls and 3 home visits **Extramural** 2/wk for 8 weeks after home training aerobic (walking and cycling (Borg BS 4)) + strength (Borg RPE 13) **Control** Standard care + breathing	1. T0 preoperative<2wk T1 postoperative wk2 T2 postoperative wk12 2. Home training 30 Intramural 10-30 Extramural 30 3. Preoperative-wk12 4. After surgery	1. 6MWT (m) mean±SD T0 677,0±89,3 / 435,8± 98,2; T1 647,5± 53,1 / 426,0±64,3; T2 705,7±65,3 / 458,2±38,6 P=0,024‡ at T2; others NR TUG (s) mean±SD T0 6,3±1,6 / 9,0±2,6; T1 4,4±2,6 / 6,0±3,2; T2 4,9±0,8 / 6,8± 1,5 P=0,041‡ at T2; others NR 2. **Drop-out** with reasons (N) 43%/38% IG: not present for testing (1), LFU (2); CG: not present for testing (2), LFU (1) **Compliance** (%) home-based NR; intramural (71; extramural (81) 3. Length of hospital stay (day) mean(range) 4(3-9) / 6(3-17); P=NR

Table 2: continued

First author, year	Study type 1(P) rehabilitation 2. Country 3. Type of study 4. Randomization	Demographics (IG/CG)	Intervention exercise (IG/CG)	Intervention 1. Measurement times 2. Exercise time (min) 3. Follow-up 4. Delivery	Outcomes (IG/CG) 1. Physical fitness 2. Patient adherence (drop-out) Exercise adherence (compliance) 3. Treatment tolerance and recovery
Hoffman 2014	1. Rehabilitation 2. United States 3. PCT 4. NA	N=5 **NSCLC** N=5 **Stage** N IIA 1, IIB 2, IIIA 2 **Age** mean±SD 63,4±7,3 **Sex** N female 3 **Treatment** N Surgery+ CT 5 **Karnofsky PS** N 70% 2, 90% 3 **Comorbidities** mean N (range) 5,4 (2-12)	**Home-based** 5/wk for 16 weeks from day 4 post-operative personalized aerobic (walking (≤3MET) + balance by Nintendo Wii Fit. Two home visits and weekly check-up calls **Control** NA	1. T0 preoperative T1 postoperative wk5 T2 postoperative wk16 2. home-training 5 + daily 5 increase 3. Baseline-wk16 4. After surgery and during CT	1. 6MWT (m) mean±SD T0 413±32; T1 382± 108; T2 463± 62 P=NR Walking time (min) mean±SD T0 NR; T1 24,0±4,3; T2 31,0±6,5 P=NR 2. **Drop-out** 0% **Compliance** %±SD(range) Walking 92,6±4,6 (87,0-98,1); Balance 94,7±7,0 (82,5-100) 3. Length of hospital stay (day) mean±SD(range) 8,4±2,6(5-12) P=NR
Kuehr 2014	1. Rehabilitation 2. Germany 3. PCT 4. NA	N=40 **NSCLC** N=40 **Stage** N IIA 2, IIIA 3, IIIB 8, IV 27 **Age** mean±SD(range) 60±12(22-75) **Sex** N(%) female 16(40) **Treatment** N Surgery 3, concurrent CHRT 4, sequential CHRT 1, CT 33	**Intramural** 5/wk for 8 weeks of which 3 times supervised aerobic (walking, cycling (Borg RPE 12-14)) + strength (resistance (Borg RPE 14-16)) **Home-based (simultaneously)** 3/wk for 8 weeks diary based aerobic (walking (Borg RPE 12-14)) + strength (resistance (Borg RPE 14-16)) and weekly check-up calls **Control** NA	1. T0 baseline T1 wk8 T2 wk16 2. Home training NR Intramural NR 3. Baseline-wk16 4. After surgery, during CHRT and CT	1. 6MWT(m) mean±SD T0 493±100;T1 525±95P<0,01;T2 543±120P=0,46 Knee flexion (Newton) mean±SD T0 140±41; T1 177±61 P<0,01; T2 192±57 P<0,01 Knee extension (Newton) mean±SD T0 201±86; T1 279±71 P<0,01; T2 327±116 P<0,01 Other muscle strengths reported but NS 2. **Drop-out** with reasons (N) 50% T0 fatigue (4), pneumonia (1), deceased (1), pain (1), infection (1), stroke (1); T1 stress (4), moved (1), metastases (1), dyspnoea (1), pneumonia (1),stopped treatment (1); T2 no time (4), LFU (5) **Compliance** (%) overall (82), home-based (77), intramural (95) 3. NR

Table 2: continued

First author, year	Study type 1(P) rehabilitation 2. Country 3. Type of study 4. Randomization	Demographics (IG/CG)	Intervention exercise (IG/CG)	Intervention 1. Measurement times 2. Exercise time (min) 3. Follow-up 4. Delivery	Outcomes (IG/CG) 1. Physical fitness 2. Patient adherence (drop-out) Exercise adherence (compliance) 3. Treatment tolerance and recovery
Quist 2012	1. Rehabilitation 2. Denmark 3. PCT 4. NA	N=29 **NSCLC** N=19 **Age** mean(range) 63(45-80) **Sex** N(%) female 16(55,2) **Treatment** N CT 27, CHRT 2 **Physical activity before diagnosis** N Sedentary (2), <3h/wk 14, ≥3h/wk 12, >4h/wk 1	**Intramural** 2/wk for 6 weeks supervised strength (resistance (70-90% 1RM)) + aerobic (cycling (85-95% max HR)) + stretching **Home-based (simultaneously)** 3/wk for 6 weeks unsupervised diary based aerobic (walking) + relaxation **Control** NA	1. T0 baseline T1 wk6 2. Home training 20-60 Intramural 90 3. Baseline-wk6 4. During CT and CHRT	1. VO2max(L/min) mean±SD T0 1,48±0,41; T1 1,57±0,41 P=0,014 6MWT (m) mean±SD T0 524,7±88,5; T1 564,0±88,6 P=0,006 FEV1 (L) mean±SD T0 1,76±0,70; T1 1,96±0,63 P=0,061 Muscle strength(kg) mean±SD Leg press: T0 70,34±26,9; T1 86,9±28,8 P=0,000; Chest press T0 30,8±13,2; T1 40,3±16,3 P=0,000; Lat machine: T0: 35,8±13,8; T1 39,2±17,6 P=0,049; Abdominal crunch: T0 24,9(10,7); T1 29,5(11,3) P=0,000; Lower back: T0 35,3±14,1; T1 43,1±16,2 P=0,000; Leg extension: T0 38,6±15,5; T1 45,1±18,9 P=0,000 2. **Drop-out** with reasons (N) 21% Loss of motivation (3), worsened PS(3) **Compliance** (%) home-based 8,7%, intramural 73,3% 3. No adverse events

Abbreviations: 6MWT=6-Minute Walking Test; Borg BS=Borg CR 10 Breathlessness Scale; BORG RPE=Borg Rating of Perceived Exertion Scale; CG=Control Group; CHRT=CHemoRadioTherapy; CI=Confidence Interval; COPD= Chronic Obstructive Pulmonary Disorder; CR=Category Ratio; CT=ChemoTherapy; CVD=CardioVascular Disease; CWCE=Constant Workrate Cycle Exercise; diff=difference; DM=Diabetes Mellitus; ESWT=Endurance Shuttle Walk Test; FEV1=Forced Expiratory Volume in 1 second; HR=Heart Rate; IG=Intervention Group; ISWT=Incremental Shuttle Walk Test; kg=kilogram; IQR=Inter Quartile Range; L=Liter; LFU=Lost to Follow Up; max=maximal; m=meter; med=median; MET=Metabolic Equivalents; min=minute; ml=milliLiter; N=Number; NA=Not Applicable; NR=Not Reported; NS=Not Significant; NSCLC=Non-Small Cell Lung Cancer; O2=oxygen; PCT=Patient Cohort Trial; PS=Performance Status; RCT= Randomized Controlled Trial; RM= Repeat Maximum; RT=RadioTherapy; s=second; SD=Standard Deviation; subj=subjects; TKI=Tyrosin Kinase Inhihibitor (targeted therapy); UK=United Kingdom; VO2max= maximal oxygen uptake; WHO=World Health Organization; wk=week; † within subjects group time effect; ‡ between subjects group time effect; § between groups; ll between measurement times

Table 3. Physical outcomes including significance and clinical relevance of changes of included studies according to measuring instruments

Outcome unit	First author year	Measurement times (IG/CG) Mean±SD; (range)				1. Absolute change [percentage] (IG/CG) 2. Mean±SD of change (range) [95%CI] (IG/CG)			1. P-value 2. Clinically relevant change*
		Baseline	Postoperative	End iv	Post iv	T0-T1	T0-T2	T1-T2	
Prehabilitation – cardiorespiratory fitness									
VO_{2max} *mL/kg/min*	Coats 2013	21,6±7,8		23,3±7,5		1. +1,7 [7,8%]			1. >0,05 2. No
VO_{2max} *L/min*	Coats 2013	1,63±7,8		1,75±0,71		1. +0,12 [+7,4%]			1. >0,05 2. No
6MWT *m*	Coats 2013	540±98		568±101		1. +28 [+5,2%] 2. +28±29			1. **<0,05** 2. No
CWCE *s*	Coats 2013	264±79		421±241		1. +57 [+59,5%] 2. +157±195			1. **<0,05** 2. yes
Rehabilitation – cardiorespiratory fitness									
VO_{2max} *mL/kg/min*	Andersen 2013	14±3		14±3		1. +0,0 [+0,0%]			1. 0,763 2. No
VO_{2max} *L/min*	Quist 2012	1,48±0,41		1,57±0,41		1. +0,09 [+6,1%] 2. +0,09 [0,02;0,16]			1. 0,014 2. NR
FEV_1 *L*	Andersen 2013	2,0±0,6		2,0±0,5		1. +0,0 [+0,0%]			1. NS 2. No
FEV_1 *L*	Brocki 2014	1,73±0,5/ 1,9±0,6		Mean diff 0,14±0,3/ 0,1±0,4	Mean diff 0,1±0,4/ 0,06±0,4	1. +0,14/+0,1 [+8,1/+5,3%] 2. 0,02 [-0,14;0,17] §	1. +0,1/+0,06 [+5,8/+3,2%] 2. 0,02 [-0,14;0,18] §	1. -0,04 /-0,04	1. T1 0,84 T2 0,84 2. No
FEV_1 *L* Quist 2012 1,76±0,7 1,96±0,6						1. +0,20 [+11,4%] 2. 0,20 [–0,01;0,41]			1. 0,061 2. No
6MWT *m*	Arbane 2011	466,6±102,1/ 455,7±98,0	D5 336,7±84,1/ 308,7± 124,8	480,2±110,0 /448,2±95,1		1. -129,9/-147 [-27,8/-32,3%]	1. +13,6/-7,5 [+2,9/ -1,6%]	1. +143,5/+139,5 [+42,6/+45,2%]	1. **<0,001**†; 0,89‡ 2. Yes

Table 3: continued

Outcome unit	First author year	Measurement times (IG/CG) Mean±SD; (range)				1. Absolute change [percentage] (IG/CG) 2. Mean±SD of change (range) [95%CI] (IG/CG)			1. P-value 2. Clinically relevant change*
		Baseline	Postoperative	End iv	Post iv	T0-T1	T0-T2	T1-T2	
6MWT *m*	Brocki 2014	427±124/ 407±102		Mean diff +61±52/ +55 ±45	Mean diff +65±70 / +60±45	1. +61±52/+55 ±45 [+14,3/+13,5%] 2. 8,33 [-20;36,27]	1. +65±70/+60±45 [+15,2/+14,7%] 2. 1,31 [-28,18;30,8]	1. +4,0/+5,0	1. T1 0,57§ T2 0,93§ 2. Yes
6MWT *m*	Granger 2013	677,0±89,3/ 435,8±98,2	Wk2 647,5±53,1 /426,0±64,3	705,7±65,3/ 458,2±38,6		1. -29,5/-9,8 [-4,4/-2,3%]	1. +28,7/+22,4 [+4,2/+5,1%]	1. +58,2/+32,2 [+9,0/ +7,6%]	1. T2 **0,024**§ 2. Yes
6MWT *m*	Hoffman 2014	413±32 (367-452)	Wk5 382±108 (202-480)	463±62 (383-529)		1. -31 [-7,5%]	1. +50 [+12,1%]	1. +81 [+21,2%]	1. NR 2. Yes
6MWT *m*	Kuehr 2014	493±100		525±95	Wk 16 543±120	1. +32 [+6,5%]	1. +50 [+10,1%]	1. +18 [+3,4%]	1. T0-T1 **<0,01** T0-T2 0,46 2. Yes
6MWT *m*	Quist 2012	524,7±88,5		564,0±88,6		1. +39,3 [+7,6%] 2. +39,3 [12,5;66,1]			1. **0,006** 2. No
ISWT *m*	Andersen 2011	NR		Med diff % +9,0(-77;39)		2. +9,0% (-77;39)			1. **0,021** 2. NR
ISWT *m*	Arbane 2014	290(180-440)/ 290(200-450)	D5 110/135	350/290		1. -180/-155 [-62/-53%]	1. +60/+0 [+21/+0%]	1. +250/+155 [+227/+115%]	1. >0,05§; >0,05 ll 2. Yes
ESWT *m*	Andersen 2011	NR		Med diff % +9(-70;432)		2. +9% (-70;432)			1. **0,002** 2. NR
Steps/day *n*	Cheville 2013	3200		4400		1. +1200 [+37,5%]			1. NR 2. NA
Walking time *min*	Hoffman 2014	NR	Wk 5 24,0±4,3	31,0±6,5		1. +7,0 [+29%]			1. NR 2. NA
TUG *s*	Granger 2013	6,3±1,6/ 9,0±2,6	Wk2 4,4±2,6/ 6,0±3,2	4,9±0,8/ 6,8±1,5		1. -1,9/-3,0 [-30,2/-30%]	1. -1,4/-2,2 1-22,2/-24,4%]	1. +0,5/+0,8 [+11,4/+13,3%]	1. **0,041**§ 2. No
Mobility *likert scale*	Cheville 2013	NR / NR		NR / NR		2.+4,88±4,66[2,96;-6,80] / +0,23±5,22[-1,76;2,22]			1. **0,002** 2. NA

Table 3: continued

Outcome unit	First author year	Measurement times (IG/CG) Mean±SD; (range)				1. Absolute change [percentage] (IG/CG) 2. Mean±SD of change (range) [95%CI] (IG/CG)			1. P-value 2. Clinically relevant change*
		Baseline	Postoperative	End iv	Post iv	T0-T1	T0-T2	T1-T2	
Activity *likert scale*	Cheville 2013	NR/NR		NR/NR		2. +1,56±5,53[-0,72;3,82] / +0,94±5,91[-1,26;3,14]			1. 0,74 § 2. NA
Prehabilitation – muscle strength									
m. deltoideus *kg*	Coats 2013	NR		NR		1. +1,82±2,83 [+18,0% ±31,0]			1. **<0,05** 2. NA
m. triceps *kg*	Coats 2013	NR		NR		1. +1,32±1,75 [+14,0%±25,0]			1. **<0,05** 2. NA
m. hamstrings *kg*	Coats 2013	NR		NR		1. +3,41±3,7 [+27,0%±40,0]			1. **<0,05** 2. NA
Rehabilitation – muscle strength									
m. quadriceps *kg*	Arbane 2011	33,2±15,2/ 29,1±10,9	D5 37,6±27,1/ 21,5±7,7	34,2±9,4/ 26,4±9,7		1. +4,4/-7,6 [+13,3/-26,1]	1. +1,0/-2,7 [+3,0/-9,3%]	1. -3,4/+4,9 [-9,0/+22,8%]	1. 0,70 ll; **0,04**§ 2. NA
Extension knee *N*	Kuehr 2014	201±86		279±71	Wk16 327±116	1. +78[+38,8%]	1. +126[+62,7%]	1. +48[+17,2%]	1. T0-T1 **<0,01** T0-T2 **<0,01** 2. NA
Extension leg *kg*	Quist et 2012	38,6±15,5		45,1±18,9		1. +6,5[+16,8%] 2. 6,5[4,1-8,9]			1. **0,000** 2. NA
Press leg *kg*	Quist 2012	70,34±26,9		86,9±28,8		1. +16,56[+23,5%] 2. +16,5[11,5-21,7]			1. **0,000** 2. NA
Extension elbow *N*	Kuehr 2014	124±44		136±44	Wk16 129±41	1. +12[+9,7%]	1. +5[+4,0%]	1. -7[-5,1%]	1. T0-T1 **<0,01** T0-T2 0,49 2. NA
Flexion knee *N*	Kuehr 2014	140±41	-	177±61	Wk16 192±57	1. +33[+23,6%]	1. +52[+37,1%]	1. +15[+8,5%]	1. T0-T1 **<0,01** T0-T2 **<0,01** 2. NA
Flexion elbow *N*	Kuehr 2014	144±52	-	152±55	Wk16 158±69	1. +8[+5,6%]	1. +14[+9,7%]	1. +6[+3,9%]	1. T0-T1 **0,02** T0-T2 0,68 2. NA

Table 3: continued

Outcome unit	First author year	Measurement times (IG/CG) Mean±SD; (range)				1. Absolute change [percentage] (IG/CG) 2. Mean±SD of change (range) [95%CI] (IG/CG)			1. P-value 2. Clinically relevant change*
		Baseline	Postoperative	End iv	Post iv	T0-T1	T0-T2	T1-T2	
Hip flexion *N*	Kuehr 2014	133±48	-	137±54	Wk16 135±62	1. +5[+3,8%]	1.+2[+1,5%]	1. -2[-1,5%]	1. T0-T1 0,21 T0-T2 0,26 2. NA
Hip abduction *N*	Kuehr 2014	153±45	-	164±48	Wk16 161±48	1. +11[+7,2%]	1. +8[+5,2%]	1. -3[-1,8%]	1. T0-T1 **<0,01** T0-T2 0,73 2. NA
Chest press *kg*	Quist 2012	30,8±13,2	-	40,4±16,3	-	1. +9,6[+31,2%] 2. +9,5[6,4-12,7]	-	-	1. **0,000** 2. NA
Lat machine *kg*	Quist 2012	35,8±13,8	-	39,2±17,6	-	1. +3,4[+9,5%] 2. +3,4[0,0-6,7]	-	-	1. **0,049** 2. NA
Abdominal crunch *kg*	Quist 2012	24,9±10,7	-	29,5±11,3	-	1. +4,6[+18,5%] 2. +4,6[3,2-6,0]	-	-	1. **0,000** 2. NA
Lower back *kg*	Quist 2012	35,3±14,1	-	43,1±16,2	-	1. +7,8[+22,1%] 2. +7,8[4,8-10,8]	-	-	1. **0,000** 2. NA

Abbreviations: 6MWT=6-Minute Walking Test; CG=Control Group; CI=Confidence Interval; CWCE=Constant workrate Cycle Exercise, D=day, diff=difference; ESWT=Endurance Shuttle Walk Test; FEV_1=Forced Expiratory Volume in 1 second; IG=Intervention Group; ISWT = Incremental Shuttle Walk Test; iv=intervention; kg=kilogram; L=Liter; m=meter; MCID=Minimal Clinically Important Difference; med=median; mL=milliliter; min=minutes; n=Number; N=Newton; NA=Not Applicable; NS=Not Significant; NR=Not Reported; s=seconds, SD=Standard Deviation; T0=baseline; T1=first measurement time; T2=last measurement time VO2max=maximum oxygen uptake; wk=week. * MCID-values for aerobic outcomes: VO2max increase of 3,5 mL/min/kg[44]; 6MWT increase of ≥42 m or 9.5% change [28]; CWCE increase of ≥100 s[45] ; FEV1 increase of 0,23L[46]; ISWT increase of 70 m[47]; ESWT increase of 154–164 m[48]; TUG (s) decrease of ≥0,8 s[49]; MCID-values not found for: Steps/day (N); Walking time (min); Mobility (likert scale); Activity (likert scale) and muscle strengths. † within subjects group time effect; ‡ between subjects group time effect; § between groups; ll between measurement times

Qualitative assessment

Only one study (9%) had a high methodological quality and was at risk for performance bias as participants nor personnel were blinded (Table 4[29]).[37] Therapeutic validity was low in this study due to insufficient eligibility criteria for therapist and setting, rationale for the training program, and monitoring or personalization of the intervention (Table 5[30]). A moderate methodological quality was found in two rehabilitation studies and one prehabilitation study (45%), where especially selection bias could influence study outcomes.[33, 39, 41] Additionally, therapeutic validity was high in all studies. In the seven remaining rehabilitation studies, a low methodological quality was found due to selection,[34, 36, 38, 40, 42, 43] reporting,[35, 36, 38, 40, 43] performance,[35-38, 40] and attrition bias.[34-36, 40, 42, 43] Of these seven studies, three had a low therapeutic validity due to lack of eligibility criteria,[35, 36, 42, 43] lack of rationale for the content and intensity of the program,[35, 43] or no personalized exercises.[36, 42, 43] The three studies assessing home-based training alone had a high therapeutic validity, and a moderate,[39, 41] and low[38] methodological quality. The interobsever agreement for methodological quality was very good (Kappa 0.80) and for therapeutic validity good (Kappa 0.76).

Table 4. Results of methodological quality according to 'the Cochrane risk of bias tool'

First author year	Randomization (selection bias)	Equal groups (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective drop-out (attrition bias)	Selective reporting (reporting bias)	Methodological quality
Andersen 2011	+	NA	NA	NA	-	-	**Moderate**
Andersen 2013	+	NA	NA	NA	+	-	**Low**
Arbane 2011	-	-	+	-	+	+	**Low**
Arbane 2014	+	-	+	+	+	+	**Low**
Brocki 2014	-	-	+	-	-	-	**High**
Cheville 2013	+	-	+	+	-	+	**Low**
Coats 2013	+	NA	NA	NA	-	-	**Moderate**
Granger 2013	-	+	+	-	+	+	**Low**
Hoffman 2014	+	NA	NA	NA	-	-	**Moderate**
Kuehr 2014	+	NA	NA	NA	+	-	**Low**
Quist 2012	+	NA	NA	NA	+	+	**Low**

Risk of bias: + ' present', - 'absent'; Methodological quality: present bias ≤ 17% 'high', 18-33% 'moderate', ≥ 50% 'low'; NA 'not applicable'

Across included studies, only one described specific demands for therapist and setting[41] and four did personalize exercises.[34, 36, 40, 41] Selective dropout in six studies could have led to attrition bias.[34-36, 40, 42, 43] Five studies did not display results entirely or did not report on significance, thereby inducing reporting bias.[35, 36, 38, 40, 43] The included randomized controlled trials did not perform blinding for randomization, participants, or personnel. Therefore, these studies were at risk for performance and detection bias.[35-38, 40]

Table 5. Results of therapeutic validity according to 'The CONTENT scale'

First author year	Description patient selection	Adequate patient selection	Eligibility criteria for therapist and setting determined and adequate	Therapeutic exercise based on a-priori aims and intentions	Rationale for content and intensity described and plausible	Intensity described	Therapeutic exercise monitored and adjusted when necessary	Exercises personalized and contextualized to individual	Adherence determined and acceptable	Therapeutic validity
Andersen 2011	+	+	-	+	+	+	+	-	+	**High**
Andersen 2013	+	+	-	+	-	+	+	+	-	**High**
Arbane 2011	+	+	-	+	-	-	+	+	-	**Low**
Arbane 2014	+	+	-	+	+	+	-	-	-	**Low**
Brocki 2014	+	+	-	+	-	+	-	-	+	**Low**
Cheville 2013	+	+	-	+	+	+	-	-	+	**High**
Coats 2013	+	+	-	+	+	+	+	-	+	**High**
Granger 2013	+	+	-	+	-	+	+	+	+	**High**
Hoffman 2014	+	+	+	+	+	+	+	+	+	**High**
Kuehr 2014	+	+	-	+	+	-	+	-	-	**Low**
Quist 2012	+	+	-	+	-	+	+	-	-	**Low**

Score: + 'performed', - ' not performed'; Therapeutic validity: high '≥ 6 times +', low '< 6 times +'

Discussion

The aim of this systematic review was to evaluate feasibility and effectiveness of prehabilitation and rehabilitation including a home-based component for patients with NSCLC and to describe physical fitness, adherence, treatment tolerance, and recovery.

Summary of evidence

Ten rehabilitation studies and one prehabilitation study were included (451 patients with NSCLC). Patients included in this review were diagnosed with stage I-IV disease, and most underwent surgery with or without (neo)adjuvant treatment (308 of 496 (62%)). However, studies in which patients received radiotherapy, chemotherapy, chemoradiotherapy, or palliative care were also included. Rehabilitation studies including a home-based component showed significantly or clinically relevant increased physical fitness. Home-based prehabilitation may increase physical fitness as well, although only one published study was found. Patient adherence and exercise adherence were generally higher and sufficient in home-based interventions compared to combinations of home-based, intramural- and/or extramural training. It remains unclear wether home-based prehabilitation can lead to less adverse events or hospitalization time, while rehabilitation including a home-based component might improve recovery after treatment.

Highest patient adherence and/or exercise adherence together with significant or clinically relevant improvements in physical fitness can be reached by home-based interventions, as was seen in three studies including home-based interventions only.[38, 39, 41] However, it should be mentioned that these were two pilot studies [39, 41] and one randomized controlled trial[38], and other included studies with a home-based component did not always report compliance of home-based exercises.[33-36, 40] Still, physical fitness did not differ between home-based training alone and those with additional extramural sessions.[37] Probably, newly diagnosed lung cancer patients show interest and motivation for exercise programs, in which home-based training during treatment was preferred.[51] As patients with NSCLC are often older and frail,[8, 9, 30] commuting and accessibility to in- and outpatient facilities hinder participation in clinic-based exercise programs.[25] Therefore, exercise programs should be delivered at the patient's own living situation to optimize adherence.[25] Furthermore, regular supervision,[52] and a personalized training program[17, 53-55] can further increase adherence rates by facilitating motivation and a physically active lifestyle, as is recognized by the CONTENT scale.[30, 31] At the time of cancer diagnosis, patients are more susceptible to persue a healthy lifestyle to optimize treatment outcomes and general health.[56] In two included studies, increased physical fitness maintained several weeks,[42] and ten months[37] after the intervention without additional exercise instructions. This was previously found in surgical patients with NSCLC receiving prehabilitation and/or rehabilitation ((p)rehabilitation), although home-based exercises were not included in these studies.[19, 57] Despite the fact that improvement of treatment tolerance or recovery is the driving force behind the concept of (p)rehabilitation, it was either not reported or reported by diverse parameters (number of complications or hospitalization days). Trials mainly included fit and selected patients without comorbidities, leaving older and high-risk patients underrepresented.[23]

Most rehabilitation studies combine intramural and/or extramural training with home-based exercises. Also, there is heterogeneity in the contents of training sessions, and their planning and sequences. Higher training intensity and use of devices such as bicycles and treadmills were more present in intramural and extramural sessions, whereas home-based sessions included lower intensity and more simple instruments. The broad patient population provided in our review included different stages of disease, treatment options, age groups, and physical fitness. This heterogeneity reflects everyday clinical care and probably explains the observed wide range of effect sizes and maximal capable improvements in treatment outcomes. However, it hinders the interpretation of summarized results, and effects of interactions between training contents and patient characteristics are warranted. Furthermore, natural physical recovery comes into play as increased physical fitness cannot be explained by the intervention solely, emphasizing the importance of control groups in studies.

Strengths and limitations

Strengths of this study are the independent literature search, selection, and data extraction by two reviewers with good agreement, thereby preventing errors in study and data selection, and limiting reporting bias.[58] Also, therapeutic validity was assessed, providing more insight in reported study outcomes, as a low therapeutic quality might explain decreased effectiveness of the intervention compared to what was expected.[30] Nevertheless, the outcomes of this systematic review should be interpreted carefully due to several contstraints. Only three studies incorporated home-based training alone for (p)rehabilitation. The eight remaining studies included home-based, intramural- and/or extramural components and as a result, seperate effects of a home-based training component could not be attributed. Also, several pilot studies were included. This means that evidence is still lacking and powered randomized controlled trials are required. Especially for home-based prehabilitation, not all potential eligible studies were available. As negative and non-significant outcomes are less likely to be published, publication bias could lead to a more positive scope of outcomes. Regarding methodological quality, cut off values were not present and categories were arbitrarily chosen. This could lead to an overestimation of methodological quality as some types of bias are determined by more than one study characteristic.[26] Moreover, some components did apply to randomized controlled trials only. Since clinical and statistical heterogeneity impeded the interpretation of patient characteristics and exercise contents, the internal validity of summarized effect sizes for the 6MWT distance is questionable. Therefore, a meta-analysis could not be performed despite the vast number of studies and patients included.[31] Furthermore, the goal of (p)rehabilitation will be different for patients receiving surgery, radiotherapy, chemoradiotherapy, chemotherapy, and palliative treatment. As the included patient group was heterogeneous with different prognoses and applied treatment regimens, various effects can be expected which cannot be explained by (lack of) effectiveness of (p)rehabilitation.

Several types of bias could influence methodological quality. Selection bias in non-randomized studies and omission of blinding participants or personnel could lead to increased motivation and more positive study results. Although it is almost impossible to perform blinding during physical interventions, one study was able to apply this on

outcome assessors and patients.[40] Attrition bias could have influenced results, although most patients indicated a reason for withdrawal. Nevertheless, some were unknown and could disguise potential negative treatment effects such as worse physical functioning or fatigue.[19, 55] Selective reporting is a concern as data regarding statistical significance were not always displayed for the home-based component specifically. Yet, evaluating whether there was a clinically relevant improvement in cardiorespiratory fitness after (p) rehabilitation was possible for all studies using the 6MWT distance. As only physical fitness was included in the search strategy, missing values for adherence treatment tolerance, and recovery were foreseen.

With regard to therapeutic validity, small sample sizes and patient cohort studies allow researchers to provide a flexible training scheme which can be easily monitored and adapted, thereby increasing patient and exercise adherence.[52, 55] As a result, effect rates could be based on individually optimized, but slightly incomparable exercise programs.[30, 31] Mainly larger studies disregard components like personalization of exercises and supervision for increasing quality and effectiveness of the intervention. Absolute training effects are more easy to compare in non-personalized fully structured training sessions,[59] resulting in higher methodological quality. However, the main goal of home-based (p)rehabilitation should be to enhance and preserve wellbeing and everyday life in patients with NSCLC.[60] Therefore, a patient tailored program with a necessity-based design should be at best interest, together with the highest therapeutical and methodological quality.[11, 23] Furthermore, all patients with NSCLC can benefit from increasing endurance and muscle strength in order to optimize treatment outcomes by home-based (p)rehabilitation. However, the selection of patients should mainly focus on older and high-risk patients and how to increase accessibility to home-based, supervised, and personalized sessions in order to maximize training, physical fitness, adherence, treatment tolerance, and recovery.[23]

In conclusion, this systematic review showed positive and encouraging results of (home-based) (p)rehabilitation on physical fitness for patients with NSCLC. Although included studies varied in quality, and quantity, results of this review indicate that combining (home-based) resistance and endurance training, as well as supervision and personalization, seem necessary to optimize physical fitness, adherence, treatment tolerance, and recovery. Although different training contexts have been included in this review, home-based training alone has not been studied extensively and several studies were underpowerd. Therefore, additional randomized controlled trials are required. This sets priority for prospective trials including older and high-risk patients with NSCLC, in which supervision, personalization, and high methodological and therapeutic quality in a home-based context are investigated. Ultimately, more evidence for home-based (p) rehabilitation can be gathered leading to improved physical fitness, patient adherence, exercise adherence, and especially recovery and treatment tolerance in this predominantly high-risk patient group.

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Part 4

Discussion and summary


10

Chapter 10

General discussion

General discussion

This thesis has shown that older patients with NSCLC received standard treatment less often and had poorer relative and overall survival compared to patients aged <70 years and those aged 65-74 years in population-based studies. Surgery and chemoradiotherapy were associated with favourable survival rates, even among elderly. However, treatment tolerance was significantly poorer among older patients receiving concurrent chemoradiotherapy compared to elderly receiving sequential chemoradiotherapy, despite that patients receiving concurrent chemoradiotherapy were relatively fitter. Patient wishes, comorbidity, and treatment tolerance should be taken into account in treatment decision-making, especially among older patients. Although geriatric assessment was not applied often in standard care, it was recognized by treating physicians that outcomes of geriatric assessment could provide valuable insights for treatment-decision making. Furthermore, prehabilitation and (home-based) rehabilitation contribute to optimizing patients with NSCLC for intensive medical treatment by improving physical fitness, treatment tolerance, and quality of life. Despite the fact that some patient characteristics in relation to treatment and outcomes were unavailable in several chapters, it seems that selected older patients can achieve similar results to younger patients and standard treatment should not be denied based on age alone. The results of this thesis are here discussed regarding clinical relevance and future perspectives. Recommendations are set for future research among the heterogeneous population of elderly with NSCLC in daily clinical practice.

Does older age make a difference in clinical practice?

Treatment patterns and survival in relation to patient characteristics

Older patients with NSCLC greatly differ from younger patients regarding performance status, comorbidity, and patient wishes.[1,2] The treatment decision-making process consists of multidisciplinary collaboration and patient assessment in the light of standard and alternative treatment options according to evidence from clinical trials.[3] However, this evidence is mainly based on younger and relatively fit patients, and high-risk patients are underrepresented.[4] This leads to biased estimations of survival and treatment tolerance, which are often not similar for fit, vulnerable, and frail patients.[2,3,5] The evidence regarding elderly patients in everyday clinical practice presented in this thesis, is highly needed and demonstrated in **part 1**. As shown in **chapter 2**, 44% of all patients diagnosed with NSCLC between 1990 and 2014 is aged 70 years or older in Dutch clinical practice. It was also shown that the proportion of patients aged ≥70 years receiving standard treatment with surgery for stage I and II, (concurrent) chemoradiotherapy for stage III, and chemotherapy for stage IV disease, has increased over time. However, stage migration could play a role, which is further explained in *Strengths and opportunities for improvement*. Relative survival was analyzed in **chapter 2,** and considered a proxy for lung cancer-specific survival, as the overall survival was adjusted for age and sex-specific survival of the general Dutch population. Between 1990 and 2014, disparities in relative survival between patients aged <70 years and those aged ≥70 years were narrowing for stage I NSCLC, remained similar for stage II, and were widening between age groups with stage III and IV NSCLC at the expense of older patients.[6]

Associations between age groups, treatment options, and survival were investigated into more detail for stage I, II, and III NSCLC. For patients with stage I specifically, **chapter 3** indicated that the proportion of patients undergoing surgical resection remained similar in 2004-2008 and 2009-2013, whereas the proportion receiving radiotherapy increased over time.[7] Although surgery was superior for elderly compared to radiotherapy in terms of long-term survival in **chapter 3**, **chapter 4** demonstrated that although short-term survival was similar between surgery and SBRT for patients aged ≥65 years with stage I and II NSCLC, long-term survival was superior for patients undergoing surgery. Nevertheless, patients aged ≥75 years with clinical stage I or II NSCLC underwent surgery less often and had poorer overall survival compared to those aged 65-74 years, even after adjustment for other prognostic factors.[8] This was also found for patients with stage III NSCLC aged ≥75 years in **chapter 5**, where chemoradiotherapy was administered less often and survival was poorer compared to those aged 65-74 years. However, survival rates were similar between age groups within treatment options.[9] Patients aged ≥85 years received standard treatment in only 33% of cases with stage I-IV NSCLC, as was indicated in **chapter 6**. However, those who received standard treatment showed similar survival outcomes compared to patients aged ≤85 years.[10]

In order to interpret these associations correctly for elderly in clinical practice, confounding by indication is important to take into consideration, as only relatively fit older patients are considered candidates for (intensive) standard treatment. Those who are unfit are more likely to receive alternative treatment options like stereotactic body radiotherapy (SBRT) or radical radiotherapy for stage I and II, radical radiotherapy for stage III, and palliative radiotherapy for stage IV NSCLC.[11,12] In **chapters 3, 4,** and **6**, it was indicated that the proportions of elderly with stage I or II NSCLC receiving SBRT and radical radiotherapy have been rising, and were associated with higher survival rates compared to those treatment options in previous years. However, survival rates remained lower compared to standard treatment options, which could be explained by the relative unfitness or vulnerability of patients receiving alternative treatment options.[7,8,10] While clinical trials imply positive disease-centered outcomes and minimal adverse events after intensive treatment, perspectives for elderly are often poorer compared to younger patients and overtreatment should be warranted. However, being too cautious with administering standard treatment to older patients puts them at risk for undertreatment. Furthermore, there should be awareness for therapeutic nihilism as it can be thought that (standard) treatment would be more harmful than beneficial to the older patient.[13] Differences in trends of standard treatment could be explained by new insights regarding combinations of current treatment strategies and adjuvant treatment in clinical practice through time. Also, advances in new treatment strategies led to the addition of driver mutations as part of standard diagnostic work-up and administering targeted therapy if applicable. Furthermore, the field of immunotherapy is rapidly evolving and currently considered as additional first-line treatment for fit and vulnerable patients,[14] with promising opportunities for future treatment strategies.[15] Other explanations for differences in proportions of administered treatment through time are improved multidisciplinary decision-making and patient involvement16,17 and more adequate staging due to improvements in diagnostic facilities.[18] The TNM guidelines were first published over 50 years ago in 1966. Changes were based on new

insights regarding prognosis[19,20] and consecutive editions became effective since 1974, 1978, 1987, 1997, 2002, 2010. The 8th edition was implemented in 2017.[19] Consequent shifts in staging for NSCLC were elaborated on at page 3 and 4 (see Histology and stage of disease in the Introduction).

Taking into account motives for omitting treatment and treatment tolerance

In **part 2, chapter 7** described that concurrent chemoradiotherapy was omitted among elderly with stage III NSCLC due to poor performance status, comorbidity, a combination of both, or refusal by patients or family.[21] Although the role of patients in treatment decision-making has not been extensively studied for stage III NSCLC, preferences and perspectives of patients with stage I and II NSCLC have been investigated. Previous studies have found that patients valued involvement in treatment decision-making,[17] and half preferred to have a collaborative role.[22] Those opting for a more active role, generally had university education and experienced worse health-related quality of life, overall well-being, sleep, and shortness of breath.[22] Also, one in five patients perceived a lack of knowledge about advantages and disadvantages of treatment options and one in four felt insufficiently involved in treatment decision-making by their physician. Although almost half of patients experienced decisional conflict and one in five felt unsure about the treatment decision, health-related quality of life was not influenced by these experiences or preferences.[17]

Older patients often present with high-risk characteristics,[23,24] leaving treatment decision-making difficult as there is a lack of evidence for treatment outcomes among elderly due to exclusion of elderly in trials, and due to slow accrual in studies specifically aimed at elderly.[25-27] **Chapters 2** and **3** demonstrated that the proportion of patients receiving best supportive care only was rather high but decreased over the years, leaving older patients untreated less often. Nevertheless, patients aged ≥70 years received less standard treatment compared to those aged <70 years in the Netherlands,6 as was the case for those aged 65-74 years compared to ≥75 years.[7] Fear of complications and poorer treatment tolerance following standard treatment could lead to altered treatment decision-making by both physicians and patients. Also, elderly can prefer less intensive treatment above standard treatment, as a good quality of life is cherished instead of longer survival time.[27-29] **Chapters 2-6** showed that elderly do suffer from poorer overall survival compared to patients aged <70 years or those aged 65-74 years. It was shown in **chapter 7** that overall survival for patients aged 70 years or older with stage III NSCLC was comparable between concurrent and sequential chemoradiotherapy. Although relatively fit and younger elderly received concurrent chemoradiotherapy, treatment tolerance was significantly poorer for those receiving concurrent compared to those receiving sequential chemoradiotherapy. However, the proportion of patients not completing intended treatment was comparable between patients receiving concurrent or sequential chemoradiotherapy.[2] A complex interplay of collinear clinical factors such as age ≥75 years,[7,8,30,31] short life expectancy,[32] poorer physical status,[33,34] and presence of comorbid conditions[11,34] could influence treatment tolerance and overall survival. More information is needed to make a proper selection of elderly patients who can benefit from standard treatment options, and those who can benefit from alternative treatment

options such as SBRT for stage I and II, or sequential chemoradiotherapy and radical radiotherapy for stage III NSCLC, taking treatment tolerance, survival, quality of life and patient wishes into account.[35-37]

How can we optimize treatment outcomes among older patients in clinical practice?

Part 3 addressed additional interventions to standard medical treatment in order to optimize treatment selection and outcomes for patients with NSCLC by geriatric assessment, and by prehabilitation and rehabilitation.

Mapping the older patient by geriatric assessment

Chronological age alone cannot encompass the dynamic and often masked conditions regarding performance, cognitive, and social status in older patients.[3,38] Therefore, it is important to broaden the assessment of each individual and take into account necessary precautions to make sure that every older patient can benefit from the most optimal treatment, which is adjusted to personal wishes as well.[39-41] Geriatric assessment is recommended in the diagnostic process of older patients with (lung) cancer,[42] as it provides insight into vulnerability, cognitive impairment, life expectancy, and risk of toxicity.[3,38,40] With this information, discontinuation and complications of intensive treatment could potentially be prevented in vulnerable and frail patients. A survey from our group evaluated current clinical practice of geriatric assessment for older patients with NSCLC according to physicians in **chapter 8**. It appeared that the implementation of geriatric assessment varied widely across the country regarding involvement of geriatricians, geriatric domains, and the use of geriatric tools.[41] Although the additive value for treatment decision-making in vulnerable and frail subgroups for both physicians and patients were uniformly recognized, [39-41] a lack of evidence of the benefits of geriatric assessment for elderly with lung cancer and logistic problems within the hospital are main barriers for the inclusion of geriatric assessment in standard diagnostic work-up.[3,39,43] Age alone should not be decisive for treatment decision-making. Therefore, outcomes of a geriatric assessment can contribute to tailored treatment choices, including the needs, interests, and values of elderly such as adverse events, completion of treatment, survival, and quality of life.[29] Some form of geriatric assessment should be included as part of standard diagnostic work-up, leading to multidisciplinary and shared treatment-decision making. Unfortunately, up until now, research has mainly focused on disease-centered outcomes in relatively fit and young patients, leading to biased expectations for the elderly regarding tolerance of treatment options and survival.[2] For patients with stage III NSCLC aged 75 years or older, these issues are addressed in the NVALT25-ELDAPT trial (NCT02284308). The primary outcome is quality-adjusted survival and treatment tolerance is incorporated as well. Also, the added value of concurrent chemoradiotherapy over sequential chemoradiotherapy is investigated among fit older patients in a randomized part of the study.[44]

Prehabilitation and rehabilitation: improving fitness in the individual patient

A marked proportion of patients with NSCLC is not fit enough to undergo standard treatment, leading to a loss of curative potential and poorer survival outcomes. This can be due to (smoking-related) comorbidities and poorer performance status.[35,45] All patients, especially the group of vulnerable or frail patients, could benefit from additional lifestyle interventions to improve fitness. The goal of lifestyle programs is to increase capacities before, during, and after medical treatment in order to improve treatment tolerance. These programs encompass physiotherapeutic interventions including strength and endurance training, combined with nutritional and psychosocial support.[46,47] Other benefits of this multidisciplinary approach are positive effects on long-term health, physical fitness, and quality of life which are worthwhile to patients as well.[48] Systematic evidence regarding (p)rehabilitation including a home-based component showed significant or clinically relevant improved physical fitness for patients with NSCLC undergoing curative treatment in **chapter 9**.[49] For surgical patients with NSCLC undergoing prehabilitation, the systematic review of the literature in **chapter 10** indicated that prehabilitation led to important beneficial effects regarding quality of life, fatigue, hospital stay, and complications.[50] The potential of these (multidisciplinary) lifestyle additions to standard medical treatment should be investigated further, especially for high-risk patients and those who are vulnerable or frail. A broader patient-centered perspective focused on subjective outcomes such as quality of life should be included in future studies as well.

Strengths and opportunities for improvement

Several studies including large numbers of patients with NSCLC were investigated in this thesis, covering the southern part of the Netherlands in **chapters 3** and **7**, as well as the entire country in **chapters 2, 4, 5,** and **6**. Also, detailed information regarding tumour characteristics and comorbidity have been collected in **chapters 3-5**, as well as motives for omitting treatment in **chapter 7**. Furthermore, treatment patterns and relative survival through time were investigated in **chapters 2** and **3**. In **chapter 8,** a questionnaire designed by expert-based consensus was administered to physicians treating patients with lung cancer. Also, available literature regarding (p)rehabilitation has been extensively investigated by two systematic reviews focusing on quantitative outcomes as well as methodological quality and physiotherapeutic validity in **chapters 9** and **10**.

Nevertheless, some limitations should be taken into consideration. Several details regarding diagnostic work-up, treatment, and outcomes would have been useful to interpret our results, but were not available for studies including data of the Netherlands Cancer Registry only (**chapters 2-6**). Protocols at the Netherlands Cancer Registry state that received treatment should be retrieved and not intended treatment, which can be interpreted as 'per protocol retrieval' instead of 'intention to treat retrieval' of data. Consequences for the interpretation of outcomes with respect to treatment are minimal for those receiving surgery, radiotherapy, or chemotherapy alone. However, for patients with stage III NSCLC receiving a combination of chemotherapy and radiotherapy, it is possible that patients who did not complete chemotherapy or did not startradiotherapy due to poorer treatment tolerance, were registered as receiving chemotherapy instead of chemoradiotherapy. As this could not be corrected for in **chapter 5**, it is possible that outcomes regarding overall survival following chemoradiotherapy were

false-positive as it represents a selection of relatively fit patients that tolerated this intensive treatment regimen. Those who could not tolerate chemoradiotherapy, were more likely to be categorized as receiving chemotherapy. In **chapter 7**, additional detailed information from medical files including completion of treatment, unplanned hospitalizations, complications, and additional patient characteristics were collected. As a result, our findings in **chapters 5** and **7** regarding treatment, treatment tolerance, and overall survival should be interpreted as survival outcomes for older patients who completed chemoradiotherapy (**chapter 5**) and as survival outcomes for patients where chemoradiotherapy was intended and not necessarily completed (**chapter 7**). For patients with stage I and II NSCLC receiving radiotherapy, only clinical stage of disease (cTNM) can be obtained and not pathological stage (pTNM). When comparing patterns of treatment and outcomes, it is important to consider the type of staging that was applied. Otherwise, comparing outcomes of surgery and radiotherapy is like comparing apples and oranges. In **chapter 3** and **4**, this was accounted for by classifying patients according to clinical stage of disease regardless of applied treatment.

Confounding by indication is an important type of bias in studies of retrospective nature. It should be warranted that treatment patterns and outcomes in relation to patient characteristics should be interpreted in the light of treatment choices that depend on factors during the time of diagnosis such as patient wishes, frailty and other factors which cannot be accounted for. Also, therapeutic nihilism is a significant underlying factor for older patients, which was previously mentioned in this discussion. Furthermore, publication bias could play a role in this specific field of research, especially in the upcoming area of prehabilitation and rehabilitation. Studies describing interventions that were not effective or did not show positive outcomes could be withheld from publishing. This leads to overestimating effects of treatment options with and without additional interventions, for which patients in clinical practice take the fall.

As **chapters 2** and **3** made use of data from the beginning of the 21st century, it should be mentioned that several important factors have changed since, such as new insights regarding effectiveness of (combinations of) treatment options, new treatment options including targeted treatment and immunotherapy, and improved patient selection. These new (combinations of) treatment options were predominantly applied among younger patients, but became more available for older patients as well in recent years. Furthermore, several changes in TNM staging guidelines were implemented throughout the years and trends in treatment and survival could be influenced. As mentioned on page 3 and 4 in the Introduction, the Will Rogers phenomenon (stage migration)51 should be taken into account. Survival rates for each stage group could be improved by changes in staging alone, and not solely due to improvements in treatment-decision making or enhances in treatment options alone. As data in **chapter 2** encompassed patients diagnosed between 1990 and 2014, and **chapter 3** included patients diagnosed between 2004 and 2013, stage migration should be bore in mind. In **chapter 2**, it was demonstrated that relative survival increased through the years for the entire population, irrespective of stage, implying that the Will Rogers Phenomenon is negligible based on these registry data. Furthermore, diagnostic work-up has improved markedly since 2009, as the PET-CT scan was incorporated into standard care. Also, patients with small tumours and metastases were diagnosed earlier as compared to the beginning of the 21st century, leading to different treatment goals and perspectives.

Future perspectives for older patients with NSCLC

Promising ongoing trials

Beneficial effects of geriatric assessment for treatment decision-making among older patients with stage III NSCLC are investigated in the NVALT25-ELDAPT-trial (NCT02284308). Also, the added value of concurrent chemoradiotherapy over sequential chemoradiotherapy is investigated among fit older patients in a randomized part of the study. The primary outcome of interest is quality-adjusted survival and it is aimed to develop a reliable and clinically applicable instrument to optimize treatment selection and outcomes for the individual older patient. [44] As of now, patients are enrolled for inclusion. Another study investigates the wellbeing of older patients with cancer in a cohort in the Netherlands and Belgium. KLIMOP includes patients aged ≥70 years diagnosed with (lung) cancer, and compares this group to patients aged ≥70 years without cancer, and to patients aged 50-69 years with (lung) cancer. Data collection is performed by interviews which includes a comprehensive geriatric assessment. Ultimately, insights in wellbeing of older patients can be gained around the time of diagnosis and treatment, and quality of life.[52] At this time, long-term measurements among enrolled patients are performed.

In order to investigate the feasibility and preliminary effects of rehabilitation for patients with NSCLC undergoing chemoradiotherapy, a lifestyle program including physiotherapeutic and nutritional interventions is offered at the start of medical treatment for patients with stage III NSCLC in the RELUC study. Patient wishes, motivation, and preferences with regard to medical treatment and the lifestyle program are extensively evaluated. This study is currently open for inclusion. Furthermore, a phase II randomized controlled trial investigates the benefits of home-based multidisciplinary exercise and supportive care among patients with inoperable NSCLC without upper age limit (ACTRN12614001268639).[53] Patients are randomized to usual care or an eight week home-based exercise program including individualized endurance, resistance, and behaviour change training. The main outcome is change in between-group difference from baseline to post-program by the six-minute walk distance. Secondary outcomes are both objective and subjective measures of physical activity, behaviour, motivation, and several domains of health-related quality of life. This trial is currently open for inclusion.

The next steps in research

Next to the awaited results of the abovementioned trials, additional evidence is highly needed for the heterogeneous older population with NSCLC in clinical practice. The definition of elderly remains ambiguous.[1,54] Therefore, patients with NSCLC from the age of 65 years onwards should be included in studies in order to encompass this broad and heterogeneous population without exclusion of those who are potentially at risk for geriatric syndromes which affect treatment tolerance, survival, and quality of life. In order to gain new insights, research approaches accustomed to elderly patients should be prioritized. As the population of elderly with NSCLC is expected to increase further in the coming years, it is of great importance to gain excellent knowledge regarding elements that should be taken into account for diagnosis, treatment-decision making,

and improving coping strategies during and after (standard) medical treatment. Also, evidence is needed regarding patient characteristics for all subgroups of elderly with NSCLC in order to gain insights into which treatment is suited best for each individual patient. A large number of patients is needed to gain knowledge on combinations of patient characteristics and related outcomes. Furthermore, the abilities and benefits of multidisciplinary lifestyle interventions should be explored and improvements in treatment tolerance, quality of life, and maybe even cost-effectiveness of the whole treatment decision-making and optimalization strategy should be investigated. For future recommendations, it is important to stimulate both elderly-specific trials and clinical trials including a larger proportion of older patients. Not only relatively fit elderly should be included, but also frail or otherwise 'disadvantaged' patients in separate studies. This can contribute to the discussion where the ideal age cut-off point should be to distinguish younger from older patients. Insights in personal treatment decision-making can be gained by investigating the joint additive value of geriatric assessment, medical treatment, and (p)rehabilitation among fit, vulnerable, and frail elderly with NSCLC (figure 1).

In order to gain knowledge regarding current clinical practice on a descriptive level and to develop clinical prediction models to guide treatment decision-making for each older patient, the whole population of patients with NSCLC in daily clinical practice should be included in a large nation-wide prospective observational cohort study. Extensive detailed information should be collected regarding diagnostic work-up and baseline characteristics (including geriatric assessment), treatment decision-making (including the role of both patients and physicians), and disease-centered as well as patient-centered outcomes (including survival, treatment tolerance, and health-related quality of life). Not only relative risks, but also absolute risks should be investigated, as absolute risk outcomes could be more informative or even preferred by the physician and individual patient above risk outcomes that are relative to other patients with NSCLC. These studies are additional to the data that are currently collected by cancer registries and contemplate to the upcoming of 'big data' analyses. Transcendent to the development of i.e. geriatric screening tools, the methods and strategies of globally known and daily-used apps could be used to design an extensive yet user-friendly tool or app, including decision trees for both patients and physicians to facilitate informed treatment-decision making. The outcomes can be tailored to specific tumour information, but also to personal preferences, short-term and long-term expectations, and disease-centered and patient-centered outcomes. Subpopulations should participate in a randomized study in order to assess effectiveness of certain treatment options among subgroups of fit, vulnerable, and frail patients. Accrual of older patients in randomized studies could be improved by a stacked randomized block design. In here, patients are first divided into homogeneous groups and then matched to similar patients based on predefined characteristics such as age, type of comorbidity, and PS. Next, the matched groups are randomized to treatment arms, leading to more specific evidence and insights for subgroups of patients. However, necessary restrictions in inclusion criteria due to risk of treatment options withhold an important part of patients from participation. Also, slower accrual can be expected in older populations with lung cancer based on previous findings,4 which underlines the importance of observational data in addition to data from randomized studies.

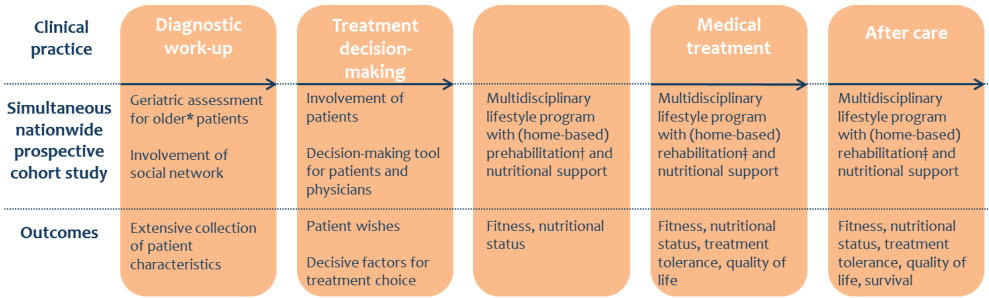

Figure 1 Flow chart of standard care in clinical practice among patients with NSCLC, supplemented with recommendations for research objectives and outcomes in simultaneous parts of standard care. * patients aged 65 years or older † therapeutic training before undergoing treatment ‡therapeutic training during and after treatment

Conclusions

The results of this PhD thesis indicated that treatment and outcomes among older patients with NSCLC in clinical practice are improving, although elderly remain disadvantaged as compared to younger patients in terms of survival. The effects of geriatric assessment for treatment decision-making are recognized by physicians in clinical practice, and effects of prehabilitation and rehabilitation on physical activity, treatment tolerance, and quality of life are promising. When patients are assessed on all relevant domains, intensive standard treatment options could be tolerated better, leading to improved short-term and long-term outcomes for each individual. As randomized clinical trials have mainly included younger and relatively fit patients, evidence-based policies and treatment guidelines for elderly with NSCLC in everyday clinical practice are highly needed.

More detailed and prospective information is necessary to develop clinical prediction models. Eventually, developments in both the medical and technical field could be combined into user-friendly treatment-decision making tools including preferences of both patients and physicians. Ultimately, better distinctions can be made between patients eligible for standard treatment and those who benefit more from alternative treatment options. By doing so, some extra personal care during the poignant time of diagnosis and treatment can contribute to improved short-term and long-term survival and quality of life for elderly with NSCLC. Improvements in treatment-decision making as well as physical fitness before and during treatment is expected to ameliorate the balance between survival and quality of life for the heterogeneous population of elderly with NSCLC in daily clinical practice.

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Chapter II

Summary

The objective of this thesis was to investigate patterns of treatment and outcomes among older patients with non-small cell lung cancer (NSCLC) in daily clinical practice. Clinical evidence for different treatment options, treatment tolerance, and survival are accumulating and promising for patients with NSCLC in general. However, evidence from clinical trials is predominantly based on the selected group of younger and fit patients without or with only few comorbid conditions. Older patients with NSCLC are heterogeneous and greatly differ from younger patients regarding performance status, comorbidity, and patient wishes. Guidelines for older patients specifically are highly needed and should include evidence regarding treatment options and outcomes with high external validity. Also, only limited evidence regarding the potential beneficial effects of geriatric assessment and therapeutic training before, during, and after medical treatment (prehabilitation and rehabilitation) is available for this population. In **chapter 1**, we presented an elaborate overview of evidence regarding treatment options, outcomes, and potentially beneficial additions to standard care for patients with NSCLC in general, as well as the lack of evidence for the older population specifically.

Part I Population-based data regarding treatment and survival

In **chapter 2**, we demonstrated that almost half of all patients diagnosed with NSCLC in the Netherlands between 1990 and 2014 was aged ≥70 years. Although this group received standard treatment options more often over time, relative survival (a proxy for lung cancer specific survival) was significantly lower compared to younger patients. Furthermore, disparities in relative survival between patients aged <70 years and those aged ≥70 years were narrowing for stage I NSCLC, remained similar for stage II, and were widening for stage III and IV NSCLC at the expense of older patients. For patients with stage I specifically, **chapter 3** indicated that the proportion undergoing surgical resection remained similar in 2004-2008 and 2009-2013, whereas the proportion receiving radiotherapy increased over time. For elderly, surgery was superior compared to radiotherapy in terms of long-term overall survival. **Chapter 4** elaborated on patients aged ≥65 years with stage I and II NSCLC, and demonstrated that although short-term survival was similar between surgery and stereotactic radiotherapy (SBRT), long-term survival was superior for those undergoing surgery. Furthermore, patients aged ≥75 years underwent surgery less often and had poorer overall survival compared to those aged 65-74 years, even after adjustment for other prognostic factors. In **Chapter 5**, we found that patients with stage III NSCLC aged ≥75 years received chemoradiotherapy less often and overall survival was poorer compared to those aged 65-74 years. However, survival rates were similar between age groups within treatment options. The oldest old patients with stage I-IV NSCLC aged ≥85 years were investigated in **chapter 6.** It appeared that only one in three patients ≥85 years received standard treatment. In the selected group that did receive standard treatment, similar survival outcomes were achieved as in patients aged ≤85 years.

- Among older patients with NSCLC in the Netherlands, increases in standard treatment and survival have been seen over time. However, the oldest patients do not always benefit to the same extent as those aged <75 years in terms of standard treatment and survival.
- Older patients often present with high-risk characteristics. Therefore, confounding by indication is an important explanation for differences in standard treatment and survival, and only relatively fit (older) patients are considered candidates for standard treatment.

Part 2 Patient characteristics for treatment tolerance and survival

In **chapter 7**, we elaborated on patients with stage III NSCLC aged ≥70 years in the south-eastern part of the Netherlands by exploring treatment choice, reasons for omission of standard treatment, treatment tolerance, and overall survival. The main reasons for omission of concurrent chemoradiotherapy were poorer performance status, comorbidity, a combination of both, or refusal by patients or family. It appeared that overall survival was comparable between concurrent and sequential chemoradiotherapy in this older population, although relatively fit and younger elderly received concurrent chemoradiotherapy more often. Furthermore, treatment tolerance was significantly poorer for those receiving concurrent compared to those receiving sequential chemoradiotherapy. However, the proportion of patients not completing intended treatment was comparable between these treatment options.

Although relatively young and fit older patients with stage III NSCLC received concurrent chemoradiotherapy, survival outcomes are similar compared to those receiving sequential chemoradiotherapy while treatment tolerance is worse.

Part 3 Optimizing treatment selection and outcomes

In **chapter 8**, we evaluated current clinical practice of geriatric assessment for older patients with NSCLC by sending pulmonologists and radiotherapists involved in this field a survey. It appeared that the implementation of geriatric assessment varied widely across the country, regarding involvement of geriatricians, geriatric domains, and the use of geriatric tools. Although the additive value of geriatric assessment for treatment decision-making in vulnerable and frail subgroups for both physicians and patients were uniformly recognized, a lack of evidence of the benefits as well as logistic problems within the hospital were main barriers for the inclusion of geriatric assessment in standard diagnostic work-up.

We examined systematic evidence regarding prehabilitation and rehabilitation including a home-based component in **chapter 9**. We found that physical fitness was improved significantly or clinically relevant among patients with NSCLC undergoing curative treatment. Furthermore, combining (home-based) resistance and endurance training, as well as supervision and personalization, seem necessary to optimize physical fitness, adherence, treatment tolerance, and recovery.

- Age alone should not be decisive for treatment decision-making. Therefore, outcomes of a geriatric assessment can contribute to tailored treatment choices, including the needs, interests, and values of older patients including quality of life. Some form of geriatric assessment should be included as part of standard diagnostic work-up, leading to multidisciplinary and shared treatment-decision making.
- Patients with NSCLC could benefit from supervised and personalized prehabilitation and rehabilitation in order to improve physical fitness, treatment tolerance, and adherence. Moreover, vulnerable and high-risk patients are expected to benefit most.

Finally, in **chapter 10**, the findings of this thesis were thoroughly discussed in relation to current literature, strengths and opportunities for improvement, and future perspectives for research with regard to older patients with NSCLC. The results of this PhD thesis indicated that treatment and outcomes among the older population are improving, although elderly remain disadvantaged as compared to younger patients in terms of survival. The effects of geriatric assessment for treatment decision-making are recognized by physicians in clinical practice, and effects of prehabilitation and rehabilitation on physical activity, treatment tolerance, and quality of life are promising. Altogether, some extra personal care during the poignant time of diagnosis and treatment could contribute to improved short-term and long-term outcomes which could ameliorate the balance between survival and quality of life for each individual within the heterogeneous population of elderly with NSCLC in daily clinical practice.


12

Chapter 12

Nederlandse samenvatting

Het doel van dit proefschrift was om de patronen van behandeling en overleving te onderzoeken bij oudere patiënten met niet-kleincellig longcarcinoom, oftewel longkanker, in de dagelijkse praktijk. In de literatuur verschijnt steeds meer wetenschappelijk bewijs over de verschillende behandelopties, behandeltolerantie en overleving bij patiënten met deze ziekte. Dit bewijs is tot nu toe gebaseerd op klinische trials waaraan voornamelijk jonge en fitte patiënten zonder comorbiditeit[1] deelnemen. De groep oudere patiënten met longkanker is heterogeen[2] en verschilt in sterke mate van jongere patiënten op het gebied van performance status,[3] comorbiditeit,[1] wensen en behoeften van de patiënt. Behandelrichtlijnen specifiek voor oudere patiënten zijn hoognodig. Hiervoor is onderzoek nodig dat bewijs levert over oudere patiënten met longkanker in de dagelijkse klinische praktijk. Daarnaast is slechts weinig bekend over de potentiële voordelige effecten van geriatrisch assessment,[4] prevalidatie[5] en revalidatie.[6] In **hoofdstuk 1** werd een uitgebreid overzicht gegeven van het beschikbare wetenschappelijk bewijs over behandelopties, uitkomsten, en de potentieel gunstige toevoegingen van geriatrisch assessment,[4] prevalidatie[5] en revalidatie[6] aan de standaardzorg voor patiënten met longkanker.

Deel I Data van de Nederlandse populatie met betrekking tot behandeling en overleving

Hoofdstuk 2 laat zien dat bijna de helft van alle patiënten die tussen 1990 en 2014 gediagnosticeerd werden met longkanker, 70 jaar of ouder waren. Ondanks dat deze oudere patiënten in de loop van de tijd vaker de standaardbehandeling kregen, bleef de relatieve overleving[7] significant slechter ten opzichte van patiënten jonger dan 70 jaar. Daarnaast is gevonden dat de verschillen in relatieve overleving tussen patiënten jonger dan 70 jaar en patiënten van 70 jaar of ouder in de loop der tijd kleiner werden voor diegenen met stadium I longkanker en gelijk bleven voor diegenen met stadium II longkanker. Deze verschillen werden echter groter voor patiënten met stadium III en IV longkanker ten koste van de ouderen. In **hoofdstuk 3** is specifiek gekeken naar patiënten met stadium I longkanker. Het percentage patiënten dat geopereerd werd, bleef gelijk tussen de tijdsperiodes 2004-2008 en 2009-2013, terwijl het percentage patiënten dat behandeld werd met (radicale) radiotherapie toenam. Ook bleek de overleving bij deze oudere populatie op de lange termijn superieur te zijn voor chirurgie ten opzichte van (radicale) radiotherapie. Patiënten met stadium I en II longkanker van 65 jaar en ouder zijn onderzocht in **hoofdstuk 4**. Hierbij bleek dat de korte-termijn overleving vergelijkbaar was tussen patiënten die geopereerd werden en diegenen die behandeld werden met stereotactische radiotherapie (SBRT). De lange-termijn overleving bleek het beste te zijn na chirurgie. Patiënten van 75 jaar en ouder werden echter minder vaak geopereerd en de overleving was slechter dan patiënten die 65-74 jaar oud waren, zelfs na correctie voor prognostische factoren.[8]

In **hoofdstuk 5** werd aangetoond dat patiënten met stadium III longkanker van 75 jaar en ouder minder vaak chemoradiotherapie ondergingen en dat de overleving slechter was vergeleken met patiënten van 65-74 jaar oud. Echter wanneer binnen de behandelgroepen de overlevingsuitkomsten vergeleken werden tussen patiënten van 75 jaar en ouder en patiënten van 65-74 jaar, dan bleek dat deze vergelijkbaar waren. In **hoofdstuk 6** zijn de oudste patiënten (85-plussers) met stadium I, II, III en IV longkanker onderzocht.

Daarvan bleek slechts één op de drie patiënten de standaardbehandeling te ontvangen. Voor de geselecteerde groep 85-plussers die wel de standaardbehandeling ontving, was de overleving vergelijkbaar met die van patiënten jonger dan 85 jaar.

- Binnen de oudere populatie in Nederland wordt meer standaardbehandeling gegeven over de tijd. Desondanks blijft de overlevingskans voor de oudste patiënten achter ten opzichte van patiënten jonger dan 75 jaar.
- Het is belangrijk om in acht te nemen dat oudere patiënten bij diagnose vaak kenmerken hebben die zijn geassocieerd met hoge(re) risico's op bijwerkingen van behandeling. De medisch specialist beoordeelt of deze van invloed kunnen zijn op de tolerantie van behandeling en het krijgen van complicaties. Bij ouderen wordt hier extra op gelet. Dit betekent dat de ouderen die wél de standaardbehandeling ontvangen, relatief fitter en gezonder zijn dan degenen die niet in aanmerking komen voor de standaardbehandeling.

Deel 2 Patiëntkarakteristieken voor behandeltolerantie en overleving

In **hoofdstuk 7** is bij patiënten met stadium III longkanker van 70 jaar en ouder onderzocht wat redenen waren voor het afwijken van de standaardbehandeling en hoe de behandeltolerantie en overleving waren. De belangrijkste redenen voor het afwijken van behandeling met gelijktijdige chemoradiotherapie waren een slechte performance status,[3] comorbiditeit,[1] een combinatie hiervan, of weigering van behandeling door de patiënt en/of familie. Ook werd gevonden dat de overleving na gelijktijdige chemoradiotherapie niet beter was dan na sequentiële chemoradiotherapie. Dit ondanks het feit dat patiënten die gelijktijdige chemoradiotherapie hebben ontvangen relatief jonger en fitter waren. Daarnaast werd gelijktijdige chemoradiotherapie slechter verdragen dan sequentiële chemoradiotherapie. De proportie patiënten die de behandeling niet kon afmaken was vergelijkbaar tussen de twee behandelopties.

- Ondanks dat juist de relatief jonge en fitte patiënten met stadium III longkanker behandeld zijn met gelijktijdige chemoradiotherapie, bleek dat de overlevingsuitkomsten vergelijkbaar waren met patiënten die sequentiële chemoradiotherapie hebben ontvangen. Ook kon de groep die gelijktijdige chemoradiotherapie kreeg dit slechter verdragen dan de groep die sequentiële chemoradiotherapie ontving.

Deel 3 Het optimaliseren van behandelselectie en uitkomsten

In **hoofdstuk 8** hebben longartsen en radiotherapeuten vragenlijsten ontvangen om de huidige standaardzorg van geriatrisch assessment[4] bij oudere patiënten met longkanker te evalueren. Het bleek dat het uitvoeren van een geriatrisch assessment[4] als onderdeel van de standaardzorg erg verschilde tussen de ziekenhuizen, met name op het gebied van het betrekken van een geriater, de getoetste geriatrische domeinen en het gebruik van geriatrische meetinstrumenten. Ondanks dat de toegevoegde waarde van geriatrisch assessment[4] voor ouderen met longkanker werd erkend door specialisten, bleken logistieke problemen en het tekort aan wetenschappelijk bewijs de belangrijkste barrières te zijn om een geriatrisch assessment[4] in de standaardzorg te implementeren.

Middels een systematische review van de literatuur zijn prevalidatie[5] en revalidatie[6] in de thuissituatie onderzocht in **hoofdstuk 9**. De fysieke fitheid bleek significant of klinisch relevant te verbeteren door (p)revalidatie.[5, 6] Daarnaast bleek dat een combinatie van krachttraining en het verbeteren van uithoudingsvermogen de beste optie is. Ook waren begeleiding en een persoonlijk trainingsprogramma erg belangrijk. Hierdoor werden de oefeningen het beste uitgevoerd en konden de meest optimale effecten bereikt worden voor fysieke fitheid, behandeltolerantie en het herstel na behandeling.

- Het uitvoeren van een geriatrisch assessment kan bijdragen aan het maken van betere behandelkeuzes die passen bij de individuele patiënt. Daarbij kan rekening gehouden worden met de behoeftes, interesses en waarden van oudere patiënten, waaronder de kwaliteit van leven.
- Prevalidatie en revalidatie vóór, tijdens en na de intensieve behandeltijd kunnen de fysieke fitheid, het verdragen van behandeling en het volhouden daarvan op peil houden of zelfs verbeteren. (P)revalidatie wordt het beste volgehouden als het programma op maat wordt gemaakt en de patiënt persoonlijk wordt begeleid. De verwachting is dat kwetsbare patiënten of diegenen met een hoog risico op complicaties het meeste baat hebben bij zo'n programma.

Tenslotte zijn de bevindingen van dit proefschrift en de klinische relevantie uitgebreid in de discussie van **hoofdstuk 10** beschreven. Hierbij zijn de uitkomsten van de hoofdstukken vergeleken met de huidige literatuur, zijn de sterke punten en kansen voor verbetering beschreven en is toekomstig onderzoek bij oudere patiënten met longkanker voorgesteld. De resultaten tonen aan dat behandeling en overleving voor ouderen met longkanker in de loop van de tijd zijn verbeterd. Ondanks deze verbeteringen blijkt echter ook dat de overleving voor oudere patiënten slechter blijft dan die van jongere patiënten. De mogelijk gunstige effecten van geriatrisch assessment[4] als onderdeel van de behandelkeuze worden erkend door medisch specialisten. Ook zijn de positieve effecten van prevalidatie[5] en revalidatie[6] op fysieke activiteit, behandeltolerantie en het volhouden van behandeling veelbelovend. In conclusie: een beetje extra zorg voor oudere patiënten met longkanker in de roerige tijd van diagnose en behandeling kan bijdragen aan het verbeteren van uitkomsten op de korte en lange termijn. Voor de individuele patiënt in deze heterogene[2] oudere populatie met longkanker kan dit de balans tussen kwaliteit van leven en overleving verbeteren.

Definities:

1 **Comorbiditeit:** Bijkomende ziekten naast niet-kleincellig longcarcinoom, zoals hart- en vaatziekten

2 **Heterogene populatie:** Een groep patiënten die bestaat uit een zeer diverse samenstelling van (patiënt- en tumor)kenmerken en daardoor lastig vergelijkbaar zijn als één universele groep

3 **Performance status:** Score om de algemene toestand van fysiek functioneren en hulpbehoevendheid in te schatten

4 **Geriatrisch assessment:** Uitgebreid onderzoek bij oudere patiënten waarbij met verschillende testen en een uitgebreid gesprek het functioneren op alle levensgebieden wordt onderzocht. Met name bij oudere patiënten wordt achteruitgang meestal niet door één probleem veroorzaakt, maar door verschillende problemen tegelijkertijd die niet altijd meteen duidelijk of zichtbaar zijn.

5 **Prevalidatie:** Extra trainen onder begeleiding van een (oncologie) fysiotherapeut vóór aanvang van de medische behandeling om het uithoudingsvermogen en kracht te verbeteren

6 **Revalidatie:** Extra trainen onder begeleiding van een (oncologie) fysiotherapeut tijdens of na de medische behandeling om het uithoudingsvermogen en kracht te verbeteren

7 **Relatieve overleving:** Een benadering van de longkanker-specifieke overleving, waarbij gecorrigeerd is voor de leeftijds- en geslachtsgebonden sterfte in de Nederlandse populatie

8 **Prognostische factoren:** Patiënt- en tumorkenmerken die voorspellend kunnen zijn voor overleving

Appendices

Valorisation
List of collaborating authors
List of publications
Dankwoord
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Valorisation

Older patients encompass a significant proportion of the Dutch population with non-small cell lung cancer (NSCLC), as half of newly diagnosed patients are aged 60-74 years and one in four is aged ≥75 years. Moreover, this proportion is expected to rise even further due to aging of 'the baby-boom offspring' and generation-specific trends in smoking behaviour. However, evidence from clinical trials and treatment guidelines are lacking for the heterogeneous elderly population with NSCLC. Therefore, it is expected that the medical field of geriatric oncology is not prepared for the approaching 'silver wave' in daily clinical practice.

This thesis demonstrated population-based trends and patterns of treatment and outcomes from different perspectives regarding elderly. Selected fit elderly can benefit from standard treatment options such as surgery and (concurrent) chemoradiotherapy to the same extent as patients under the age of 70 or those aged 65-74 years. However, it should be borne in mind that older patients are not always willing to undergo intensive treatment and an important proportion of patients is not able to undergo intensive treatment due to poor performance status or comorbid conditions. Important additions to standard care are geriatric assessment and therapeutic training before, during, and after treatment (prehabilitation and rehabilitation). These additions could optimize and personalize treatment decision-making, as well as patient and disease-centered outcomes.

The research papers included in this thesis were presented during several (inter)national conferences in order to share relevant and new insights to other professionals in the research field. At the 16th World Conference of Lung Cancer (WCLC) in Denver, Colorado in 2015, the results of **chapter 7** were introduced. The conference of the International Society of Geriatric Oncology (SIOG) was attended in Milan in 2016, where our findings shown in **chapter 9** were demonstrated. In 2018, the outcomes of **chapter 4** were presented at the SIOG conference in Amsterdam. During the course of this PhD thesis, the results of **chapter 2** and **chapter 9** were introduced at several meetings of the Dutch Collaboration for geriatric oncology, and **chapter 2** and **chapter 7** were displayed at invitational conferences of the Oncology Policy Committee in VieCuri Medical Centre. At the annual research symposium in VieCuri Medical Centre, the findings of **chapter 2** and **9** were demonstrated in 2016, **chapter 7** in 2017, and **chapter 4** in 2018.

The external validity of cohort studies in this thesis was high due to the veracious reflection and high generalizability of included patients as compared to the proposed population. As a result, insights from real-life patients and real-life outcomes including survival, treatment tolerance, and physical fitness could be obtained. The primary impact of this thesis focuses on the understanding of treatment patterns in relation to survival among unselected elderly in daily clinical practice. Also, these outcomes can serve for informational and educational purposes, as well as new perspectives for future research objectives. As this thesis includes primarily observational and retrospective data, prospective data are necessary to further elaborate on causal relationships and the effectiveness of treatment options based on patient- and disease-centered outcomes.

Special attention is needed for patient accrual in elderly-specific studies, as vulnerability and fear of potential risks often lead to refusal of participation. The older population is expected to expand rapidly in the nearby future, and impactful research is highly needed for these patients with NSCLC.

In summary, the value of this thesis lays in the new insights specific for the older population, thereby informing professionals in this multidisciplinary field regarding patterns of treatment and outcomes among older patients with NSCLC in daily clinical practice. Colleagues in the academic and hospital setting have access to the published papers, providing evidence with scientific integrity as a stepping stone to clinical research and future guidelines. More importantly, these papers can contribute to the conversation regarding treatment perspectives and wishes between physicians and older patients with NSCLC in future clinical practice.

List of collaborating authors

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List of publications

Population-based patterns of treatment and survival among patients aged ≥65 years with stage I-II non-small cell lung cancer.
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Curriculum Vitae

Lizzy (Elisabeth Johanna Margaretha) Driessen was born on October 29th 1991 in Venlo. Lizzy grew up in the nearby town Baarlo where she finished primary school. In 2004, she continued her education in the VWO+ class at het Bouwens van der Boijecollege in Panningen. She attended Gymnasium in the second and third year, followed by Atheneum in the last three years with a curricular focus on nature, health, and sciences. She graduated secondary school in 2010, and started the bachelor Biomedical Sciences at Radboud University in Nijmegen. She lived in Nijmegen from 2011 until 2014 and moved back to Baarlo after finishing her bachelors' degree in 2014. Next, Lizzy continued with the two-year research master Biomedical Sciences at Radboud University focusing on the major Epidemiology and the Communication profile. She also followed a minor Health Education and Promotion at Maastricht University. Lizzy obtained her Master of Science degree in August 2015 after completing her research internship at VieCuri Medical Center in Venlo, where she was inspired to continue in the field of clinical epidemiology by Prof. dr. M.L.G. Janssen-Heijnen.

After her Masters' graduation, Lizzy was employed as a medical researcher at the Science Desk at VieCuri Medical Center in Venlo, focusing on research, education, and consultancy across the hospital. Meanwhile, she started her PhD trajectory in November 2015 at the department of Clinical Epidemiology at VieCuri Medical Center in Venlo and was also appointed at the Department of Epidemiology at Maastricht University. Her research was focused on 'Older patients with non-small cell lung cancer in daily clinical practice: Optimizing treatment selection and outcomes'. This resulted in the present thesis, where pleasant collaborations with inspiring professionals were achieved with Zuyderland Medical Center Heerlen, Maastricht University Medical Center, MAASTRO clinic, the Netherlands Comprehensive Cancer Center, Maastricht University, Elisabeth TweeSteden Hospital, Adelante, the Diakonessenhuis, Utrecht Medical Center, and Amphia Hospital. Lizzy finished her PhD in December 2018, and lives with her partner Ruud Boumans in her hometown Baarlo.

PhD portfolio

Name PhD student EJM Driessen

Affiliation Department of Clinical Epidemiology, VieCuri Medical Center
Department of Epidemiology, Maastricht University

PhD period November 2015- December 2018

Courses	**Year**
Good Clinical Practice, EMWO	Dec 2015
Basic Life Support, VieCuri MC	May 2016
Clinical prediction models, UM	May 2017
Masterclass meta-analysis, STZ	Mar 2018

Oral presentations	
Wetenschapsbijeenkomst VieCuri MC	Jun 2015
Oncologie Beleidscommissie, VieCuri MC	Aug 2015
2x Gerionne/werkgroep kanker bij ouderen, IKNL/KWF	Aug 2016
Wetenschapsbijeenkomst VieCuri MC	Okt 2016
2x Wetenschapsavond VieCuri MC	Nov 2016
Centrale WetenschapsCommissie VieCuri MC	Jan 2017
Wetenschapsbijeenkomst VieCuri MC	Apr 2017
Wetenschapsavond VieCuri MC, winner Best Research Publication of 2016	Dec 2017
Wetenschapsbijeenkomst VieCuri MC	Jan 2018
SIOG 2018	Nov 2018

Poster presentations	
1 poster Wetenschapsavond VieCuri MC	Dec 2015
1 poster SIOG	Nov 2016
2 posters Wetenschapsavond VieCuri MC	Dec 2016
1 poster Wetenschapsavond VieCuri MC	Nov 2018

Courses	**Year**
(Inter)national conferences, seminars, and other conferences	
16th WCLC, Denver, USA	Jun 2015
Oncologiesymposium, Maastricht, the Netherlands	Nov 2015
Symposium Onderzoek in beweging, Maastricht, the Netherlands	Feb 2016
Jubilieumsymposium Geriatrie, Baarlo, the Netherlands	Jun 2016
Gerionne/werkgroup kanker bij ouderen, IKNL Utrecht	Aug 2016
SIOG, Milan, Italy	Nov 2016
Wetenschapsavond VieCuri MC	Nov 2016
Epidemiology-Go your own way, Utrecht, the Netherlands	Mrt 2017
Gerionne/werkgroup kanker bij ouderen, IKNL Utrecht	Mrt 2017
Oratie Prof. dr. MLG Janssen-Heijnen, Maastricht University	Jun 2017
9e Invitational Conference Oncologie	Feb 2018
Oncologie symposium 'Ouderen met kanker', MUMC+	Mrt 2018
SIOG, Amsterdam, the Netherlands	Nov 2018

Other tasks in VieCuri Medical Center	**Period**
Research consultant (i.e. supervisor statistical analyses, guiding study design and execution, procedure local approval procedure)	Aug 2015- Dec 2018
Teaching courses (i.e. Statistics & SPSS, Critical Review of Literature)	
Project design and management of RELUC (early Rehabilitation for patients with stage III non-small cell LUng cancer undergoing Chemoradiotherapy)	2016-2018

Other publications	
Dutch journal of Oncology (NED TIJDSCHR ONCOL 2017;14:151-5): Study protocol of The NVALT25-ELDAPT trial: selection of the optimal treatment for the older patient with stage III non-small cell lung cancer	Jun 2017
Newsletter Research of Netherlands Comprehensive Cancer Center: Verschillen in relatieve overleving lopen op tussen jong & oud met NSCLC	May 2017
Newsletter Medical Specialists of Netherlands Comprehensive Cancer Center: Toename behandeling en overleving NSCLC; verschil met oudere patiënt blijft	Feb 2018